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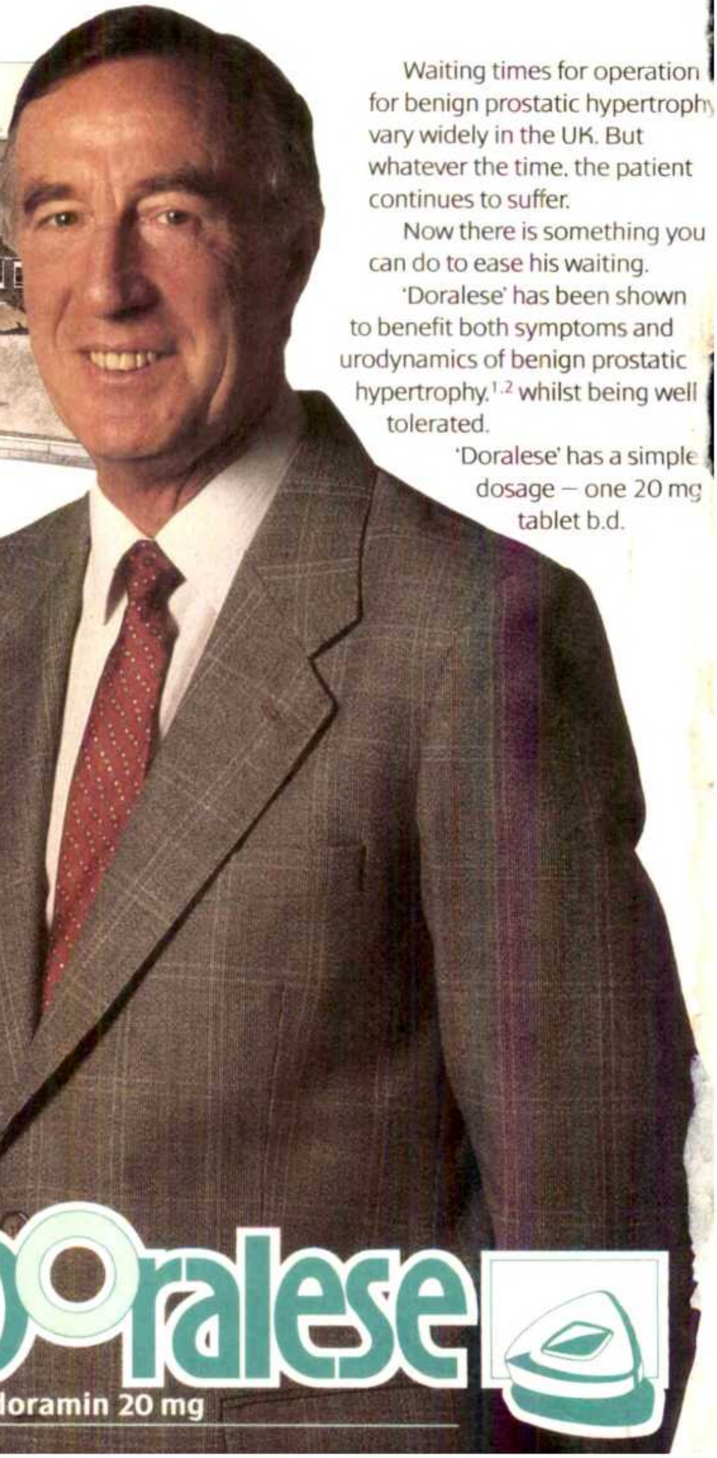

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The Changing Practice of Percutaneous Stone Surgery. Review of 1000 Cases 1981–1988

D. J. JONES, G. L. RUSSELL, M. J. KELLETT and J. E. A. WICKHAM

St Paul's Hospital and Institute of Urology, London

Summary—A review was carried out on 1000 cases of percutaneous nephrolithotomy (PCNL), Group 1 (500), 1981–1985, being compared with Group 2 (500), 1985–1988. Previous renal surgery had been performed in 17.4% of patients in Group 1 and 36% in Group 2. There were 17.2% complicated patients in Group 1 and 51% in Group 2. The stone burden included 30.2% multiple, partial staghorn and staghorn calculi in Group 1 and 47.2% in Group 2. The use of *in situ* stone disintegration increased from 22.2% in Group 1 to 73.4% in Group 2 and nephrostomy drainage was necessary in 29.6% compared with 75%. Post-operative complications increased from 13.6 to 24%. Stone-free rates decreased from 92 to 51%, but the addition of other methods of treatment and the inclusion of patients with stone fragments of 2 mm or less increased these figures to 98% in Group 1 and 83% in Group 2.

More complicated patients with complex stones are now being referred for PCNL. These patients require multiple treatments, including extracorporeal shock wave lithotripsy (ESWL) and percutaneous surgery, in combination with other endoscopic and radiological procedures.

Percutaneous removal of a renal stone was first reported by Rupel and Brown (1941). Brantley and Shirley (1974) performed stone extraction using a Dormia basket for retained renal stones in the post-operative period and Fernstrom and Johanson (1976) described the removal of renal stones in 3 patients under radiological control via a nephrostomy tube. Following these early descriptions, urologists in England and West Germany developed the technique of percutaneous nephroscopy and stone extraction under direct vision (Alken *et al.*, 1981; Wickham and Kellett, 1981a and b). In early series of patients undergoing this technique, the success rates ranged from 71 to 91% (Whitfield, 1983; Wickham *et al.*, 1983a and b; Clayman *et al.*, 1984; Whitfield and Mills, 1985).

A success rate of 98.3% was subsequently reported from the Mayo Clinic (Segura *et al.*, 1985) in a series of 1000 patients, although only 805 of these patients had renal calculi. The majority of stones reported in these series were small and suitable for simple extraction. Lee *et al.* (1986) reported a success rate for such simple stones of 98% and for staghorn calculi 87%, in a series of 500 patients. Payne *et al.* (1985) reviewed 450 patients undergoing PCNL with successful removal in 92% at the first procedure, rising to 98% with subsequent PCNL.

More recently, workers have compared the results of ESWL and PCNL or a combination of these treatments in an attempt to define efficacy, cost and complication rates (Charig *et al.*, 1986; Dickinson *et al.*, 1986; Lingeman *et al.*, 1987). Whilst there is no strong consensus of opinion regarding the best treatment for calculi, there is general agreement that for difficult stones a combination of treatments is necessary. There has, however, been a suggestion recently that PCNL may be preferable to ESWL and that investment in lithotripsy facilities may be inadvisable (Mays *et al.*, 1988).

In view of the fact that many of the high success rates and low complication rates reported from

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various PCNL series were based on simple stones and that the expectations of patients and referring doctors may thus be falsely raised by these figures, we reviewed 1000 patients who had undergone PCNL to see whether the patients being referred, their stone burden, the success and complication rates had changed, at a time when ESWL was rapidly developing and possibly treating the more simple stones.

Patients and Methods

The study group comprised 1000 patients undergoing PCNL at St Paul's Hospital between 1981 and 1988. They were divided into 2 groups of 500: Group 1 patients underwent PCNL between 1981 and 1985 and Group 2 patients between 1985 and 1988. The technique of PCNL has been well described (Alken *et al.*, 1981; Wickham and Kellett, 1981a and b) and the early patients in Group 1 had a 2-stage procedure and stone extraction via a Dormia basket. The remaining patients in Group 1 and all patients in Group 2 had a single-stage procedure, with simple stones being extracted using alligator or triradiate forceps and larger stones being disintegrated by means of ultrasound or electrohydraulic lithotripsy (Miller *et al.*, 1983, 1984a and b; Wickham *et al.*, 1984). All patients received prophylactic antibiotics and PCNL was routinely performed under general anaesthesia. Retrograde placement of a ureteric catheter for introduction of contrast media or to flush a ureteric stone was used routinely when possible (Kellett *et al.*, 1985).

Table 1 Age, Sex, Stone Distribution and Previous Surgery

	Group 1 (%) (n=500)	*Group 2 (%) (n=500)*
Male	287 (57.6)	273 (54.4)
Female	213 (42.4)	227 (45 6)
Left-sided	272 (54.5)	281 (56)
Right-sided	228 (45.5)	211 (44)
Age range (years) (mean)	5–89 (43.2)	13–83 (48.4)
Previous renal surgery	87 (17.4%)	180 (36%)

Table 2 Stone Burden

Stones	*Group 1 (%) (n=500)*	*Group 2 (%) (n=500)*
Solitary < 10 mm	238 (47.6)	132 (26.4)
Solitary > 10 mm	111 (24.2)	132 (26.4)
Multiple	68 (13.6)	91 (18.2)
Partial staghorn	32 (6.4)	46 (9 2)
Staghorn	51 (10.2)	99 (19.8)

Table 3 Complicated Cases

Complications	*Group 1 (n=86)*	*Group 2 (n=255)*
Solitary	19	34
Horseshoe	3	12
Transplants	1	5
Stoma	14	33
Paraplegia	2	12
Gross obesity	3	14
Serious medical conditions	44	145

Results

The characteristics of the 2 groups are shown in Table 1, revealing a preponderance of males and left-sided stones. The mean age in Group 2 was greater by 5 years (43.2 versus 48.4 years). The stone burden is shown in Table 2, with an increase in patients with large, multiple or complex stones in Group 2. The number of patients with complicated problems either of a renal or general medical nature has also increased and the details are shown in Table 3. Serious medical conditions included chronic renal failure, abnormal clotting disorders, skeletal deformities, severe respiratory problems, diabetes, ischaemic heart disease, leukaemia, neurological disorders and there were 3 patients who were Jehovah's Witnesses. The technique of stone removal evolved during the period of this study with increasing radiological and endourological expertise and the use of more sophisticated purpose-designed instruments (Miller and Wickham, 1983; Miller *et al.*, 1984a and b). The 2-stage technique for PCNL was used in 183 patients (33.6%) in Group 1 and then abandoned.

The details of operative technique for access and stone removal are shown in Table 4. Per-operative complications were experienced in 138 patients (27.6%) in Group 1 and 89 (17.8%) in Group 2. Significant perforation of the renal pelvis or calices was seen in 74 patients (14.8%) in Group 1 but in only 20 (4%) in Group 2. The incidence of per-operative bleeding sufficient to prolong the surgery or cause it to be abandoned remained unchanged, occurring in 64 patients (12.8%) in Group 1 and 58 (11.6%) in Group 2. Other complications such as equipment failure, stones being flushed down the ureter, failure of a ureteric "push" (Kellet *et al.*, 1985), Amplatz tube misplacement and difficulties due to skeletal deformities were similar in both groups, with 27 (5.4%) in Group 1 and 25 (5%) in Group 2. Post-operative complications increased, occurring in 68 patients (13.6%) in Group 1 and 120 (24%) in Group 2. The details of these complications are shown in Table 5. Sepsis was defined as the presence of a significant pyrexia necessitating the use of parenteral antibiotics. Transfusion requirements were greater in Group 2, but the majority of patients transfused required 2 to 3 units only. Six patients required massive transfusion (8–14 units) and embolisation under radiological control was successfully carried out in all 6. Of the 3 deaths in Group 1, 2 were due to myocardial infarction and 1 patient died of overwhelming sepsis in the immediate post-operative period. In Group 2, 3 of the deaths were from myocardial infarction and the remaining patient, an 82-year-old female with bilateral staghorn calculi and chronic renal failure, died of bronchopneumonia.

More than 1 PCNL procedure was necessary in 28 patients (5.6%) in Group 1 (27 patients (2 procedures), 1 patient (3)) and 80 patients (16%) in Group 2 (71 patients (2), 7 patients (3), 2 patients (4)). Open surgery was subsequently required in 32 patients in Group 1 (nephrectomy (1), nephrolithotomy (11), pyelolithotomy (9), ureterolithotomy (11)), almost all in the earlier cases. Thirteen patients in Group 2 required open surgery: 3 underwent nephrectomy and 1 a partial nephrectomy for what were deemed to be poorly or non-functioning kidneys still containing stones after PCNL. In addition there were 2 nephrolithomies, 2 pyelolithotomies, 1 pyeloplasty, 2 ureterolithotomies and 1 ureteric stricturoplasty. The success rates, as defined by the patients being stone-free or having fragments of 2 mm or less, are shown in Table 6. Whereas 92% of patients were rendered stone-free in Group 1 by PCNL alone, only 51% of patients in Group 2 had complete stone clearance. The addition of other methods of treatment in this group (ESWL (139 patients), ureteroscopy (35), open surgery (11)) increased the stone-free rate to 59%, with a further 24% having fragments of 2 mm or less. Thus with a combination of all treatments, 98% in Group 1 and 83% in Group 2 eventually became stone-free or had fragments of 2 mm or less.

Table 4 Per-operative Techniques for Access and Stone Removal

Techniques	*Group 1*	*Group 2*
Two-stage	183	0
Failed access	73	25
>1 puncture	32	107
Dormia basket	68	0
Alligator/triradiate forceps	321	133
US/EHL disintegration	111	367
Nephrostomy drainage	148	375

Table 5 Post-operative Complications

	Group 1	*Group 2*
Patients	68 (13.6%)	120 (24%)
Sepsis	28	47
Transfusion	29	55
Ureteric obstruction	21	10
Embolisation	2	4
Others (Chest infection, pain, gross haematuria, urethral stricture, ureteric stricture, pulmonary oedema, acute renal failure)	8	26
Deaths	3	4

Table 6 Success rates from PCNL alone and PCNL and other Procedures (ESWL, URS and laser, open surgery)

	Group 1 (%)		*Group 2 (%)*	
After PCNL only				
Stone-free	460	466 (93.2)	255	328 (65.8)
2 mm fragments or less	6		73	
>2 mm fragments	34 (6.8)		172 (34.2)	
After PCNL ± other procedure				
Stone-free	487	493 (98.6)	295	415 (83)
2 mm fragments or less	6		120	
>2 mm fragments	7 (1.4)		85 (17)	

Discussion

Early enthusiastic descriptions of PCNL, with reports of high success rates from large series of patients in Europe and the USA between 1980 and 1985, led to increasing numbers of patients being referred to centres which specialised in percutaneous surgery. The surgeons and general practitioners referring these patients had high expectations that this treatment would be successful in removing the stones and result in shorter hospital stays with a more rapid and pain-free convalescence than was expected after open surgery. In addition, complication rates appeared to be low.

The series reported were mainly of patients with small simple stones eminently suitable for a straightforward lift-out procedure. Less attention was paid, however, to the larger complex stones or the unfit patient that may present with these stones. As PCNL was developing, ESWL was rapidly becoming an accepted and established technique for the treatment of renal stones. Many patients with small simple stones, initially referred for PCNL, were effectively treated by ESWL. The resulting complex stones were proving difficult to treat by PCNL alone and we were disturbed at suggestions that PCNL alone should be effective in the majority of cases (Mays *et al.*, 1988). We were also aware that many of our patients and their referring doctors were disappointed that the treatment was often prolonged, complex and unsuccessful. The reasons for this are multifactorial but due mainly to the patients being more unfit and the stone burden greater.

Whilst there is only a small increase in the age of the patients in the later group, there is no doubt that the patients now presenting have a much higher incidence of other medical problems (which may indeed have been the cause of their stones). The presence of these problems obviously necessitates a more rigorous pre-operative preparation and also increases the likelihood of post-operative morbidity and mortality. It is interesting that the presence of solitary or horseshoe kidneys has not been associated with an increase in the number of complications. Gross obesity is a relative contraindication to open surgery and due to imaging failure and machine inadequacy may also be an absolute contraindication to ESWL. Similarly, obesity causes problems with PCNL due to imaging failures and instruments that may be too short to reach the stone or even the kidney.

The stone burden has increased both in size and complexity. This is reflected in the increased need for multiple punctures during a PCNL session, the almost 3-fold increase in patients requiring multiple PCNL sessions and a similar increase in the number of patients requiring *in situ* disintegration by ultrasound or electrohydraulic lithotripsy.

Failed access has become much less of a problem (only 5% in Group 2) and this must be due to increased radiological expertise. Per-operative complications have also decreased as a result of the development of more sophisticated purpose-designed instruments and improved operator expertise. In a centre with a teaching commitment there will inevitably be a learning curve effect on the numbers of such complications. The increase in post-operative complications from 13.6 to 24% is a factor of the need for longer and more complex procedures in often unfit patients.

The reduction in the number of patients rendered stone-free or left with small fragments, from 93 to 65% with PCNL alone, is disappointing but inevitable with increased stone burden and complexity. It is encouraging that with the addition of ureteroscopy, lasertripsy, ESWL and occasionally open surgery, the success rate rises to 83%.

This study confirms our suspicions that the practice of percutaneous stone surgery is changing and shows that complex stones now being referred and the patients with complex medical problems represent a considerable challenge to urologists, radiologists and their medical colleagues. It is clear that this challenge will inevitably result in higher complication rates and lower success rates than previously reported.

PCNL alone is unlikely to render these patients stone-free and suggestions that it be used in preference to ESWL are clearly spurious. PCNL must be viewed only as part of the management, in conjunction with ESWL and other radiological and endourological techniques.

Acknowledgement

We are grateful to Miss Sarah Read for typing the manuscript.

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The Authors

D J Jones, FRCS, formerly Senior Registrar in Urology, St Paul's Hospital. Now Consultant Urologist, The Princess of Wales RAF Hospital, Ely.

G. L Russell, FRACS, formerly Senior Registrar in Urology and Australasian Fellow, St Paul's Hospital Now Senior Registrar in Urology, Norfolk and Norwich Hospital, Norwich.

M J. Kellett, MD, FRCR, Consultant Radiologist, St Paul's Hospital

J. E A Wickham, MS, FRCS, Consultant Urologist, St Paul's Hospital, Director, Academic Unit, Institute of Urology.

Request for reprints to· Wing Commander D. J. Jones, The Princess of Wales RAF Hospital, Ely, Cambs CB6 1DN

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Lithotripsy for Calculi in Caliceal Diverticula?

A. W. S. RITCHIE, N. J. PARR, S. A. MOUSSA and D. A. TOLLEY

The Scottish Lithotriptor Centre, Deaconess Hospital, Edinburgh

Summary—There is continuing debate about the optimum management of patients with calculi in caliceal diverticula. Extracorporeal piezoelectric lithotripsy (EPL) has the advantage of being non-invasive, whereas endourological management can treat the underlying anatomical problem. A total of 20 patients with calculi in caliceal diverticula were treated with EPL. Twelve of 16 patients with symptoms (75%) were rendered symptom-free but only 5 (25%) became stone-free.

This information should be of value in counselling patients before selecting the appropriate treatment.

Pyelo-caliceal diverticula may be congenital or acquired malformations of the collecting system. The cavity, lined by transitional epithelium, is connected by a channel of varying diameter to a calix or the renal pelvis (Abeshouse and Abeshouse, 1963). The incidence of caliceal diverticula in IVU series has been reported as between 0.2 and 0.4% (Middleton and Pfister, 1974; Timmons *et al.*, 1975). Calculi have been reported to develop in up to 50% of such diverticula (Yow and Bunts, 1955) but the natural history of such malformations, with or without calculi, is unclear.

Before the development of percutaneous surgery and extracorporeal shock wave lithotripsy (ESWL), open surgical dissection and removal was recommended only in the presence of symptoms or complications. With the advent of less invasive treatments, the threshold for intervention has been lowered.

Previous reports of the results of ESWL for calculi in caliceal diverticula have produced opposing views on the efficacy of such treatment. Psihramis and Dretler (1987) reported 10 patients and stated that ESWL was an appropriate treatment because of its safety, low morbidity and acceptable likelihood of symptomatic relief (70%). Conversely, Thuroff and Alken (1988), in a report of 16 patients, stated that ESWL "does not seem to be the best choice for treating stones in caliceal diverticula" on account of inadequate stone disintegration and unpredictable clearance of the fragments. ESWL and EPL do not, of course, treat the underlying anatomical abnormality.

Percutaneous surgery or transureteric approaches are more invasive and may be technically demanding but do allow for more certain stone removal and obliteration of the diverticulum or dilatation of the channel into the collecting system (Hulbert *et al.*, 1986; Thuroff and Alken, 1988).

We have reviewed our experience with piezoelectric lithotripsy for calculi in caliceal diverticula, in an attempt to determine the place of EPL in the management of this condition.

Patients and Methods

Between September 1987 and April 1989, calculi in 827 kidneys were treated with EPL. Twenty patients (10 male) had treatment for calculi in caliceal diverticula. The Figure illustrates the typical radiographic appearance. The age range of the 20 patients was 21 to 91 years (mean 48). Twelve calculi were in the left kidney; 7 were related to the middle calix, 7 to the lower calix and 6 to the upper calix. The calculi ranged in maximum diameter from 5 to 15 mm (mean diameter 9).

Details of treatment

Treatment was performed using a Wolf Piezolith 2300. This second generation lithotriptor uses

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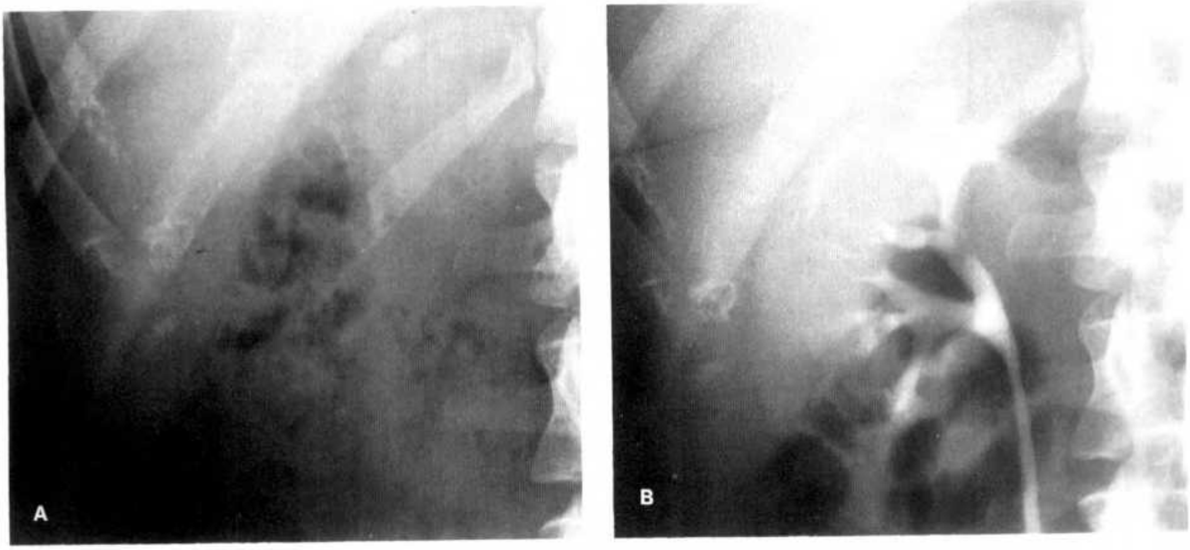

Fig. Plain X-ray (A) and X-ray after contrast (B) of typical calculus in a caliceal diverticulum related to the upper calix.

ultrasound to localise the calculus and piezoceramic technology to generate the shock waves (Marberger *et al.*, 1988; Neerhut *et al.*, 1989). Patients were treated without sedation or anaesthesia. They received on average 2 sessions of EPL (range 1–5). The average number of shock waves was 6530 (range 1500–14,500). There were no preliminary procedures.

Follow-up X-rays were performed immediately after lithotripsy and were available after this date in all but 2 patients, who did not attend for follow-up after becoming symptom-free. All patients were interviewed, if necessary by telephone, to establish their progress and symptoms following treatment.

Results

The incidence of caliceal diverticula in the treated kidneys was 2.4% (20/827). The mean follow-up interval from the last treatment session was 117 days (range 0–468).

Symptoms

Sixteen patients had symptoms before EPL; 11 of these complained of pain, 3 had pain and recurrent urinary infection, 1 had pain and haematuria and 1 had recurrent urinary infection. Following EPL, 12 of these patients (75%) have no symptoms (mean follow-up from last treatment to last interview 241 days, range 50–520), 1 has occasional discomfort and 3 have persistent troublesome pain, 2 of whom are stone-free.

Four patients had no symptoms before EPL and remain asymptomatic.

Fragmentation and clearance

Post-treatment radiographs showed evidence of stone fragmentation in all patients; 5 (25%) became stone-free following EPL and 6 have residual fragments of 2 mm or less. The remainder have larger fragments. One patient has had a partially fragmented calculus removed by percutaneous surgery and 1 patient with persisting pain awaits percutaneous extraction. The clearance rates for caliceal calculi of similar size and treated during the same period are shown in the Table.

Having cleared the stone fragments resulting from lithotripsy, 1 patient developed an inflammatory mass at the site of the diverticulum and has since been managed by partial nephrectomy.

Table Comparison of Results of Lithotripsy for Single Caliceal Calculi (5–15 mm) and Calculi in Caliceal Diverticula

	No.	*Overall stone-free (%)*	*Stone-free at 3 months (%)*
Upper calix	28	61	83
Middle calix	34	62	94
Lower calix	170	54	73
All caliceal diverticula	20	25	40

Discussion

The presence of a caliceal diverticulum is not always obvious and some of our patients were diagnosed only when failure of stone clearance prompted repeat contrast studies with or without tomography. This fact underlines the need for good quality contrast studies to establish detailed renal anatomy before commencing lithotripsy.

Our enthusiasm for this new technology led us to treat 4 patients without symptoms. None became stone-free and although the natural history of their condition without treatment is uncertain, we would no longer treat such patients as a routine.

Of those with symptoms, 75% became symptom-free—a figure similar to that reported by Psihramis and Dretler (1987). The future duration of symptomatic relief is uncertain but it is likely that with residual stone fragments, new stones will be formed in the majority of cases.

Review of the radiographs in our patients did not reveal any factors which would enable us to predict which patients would become stone-free or derive symptomatic benefit. It remains possible that such prediction may be assisted by better quality imaging (*e.g.* retrograde contrast studies with oblique views and tomography), although this would be more invasive for the patient.

Although more invasive for the patient and demanding for the surgeon, endourological approaches to such calculi seem more likely to be successful in the long term. Hulbert *et al.* (1986) reported successful removal of calculi in caliceal diverticula in 10 of 10 patients (some requiring 2 procedures) and successful obliteration of the diverticulum, when the puncture was made directly on to the calculus. Thuroff and Alken (1988) successfully removed 15 of 16 calculi in diverticula and connections to the collecting system were dilated in 14. There are, however, no studies directly comparing treatment by ESWL/EPL and endourological techniques.

If the patient does not wish to consider an endourological approach, then he/she can be counselled that EPL offers a 75% chance of symptomatic relief. The probability of becoming stone-free following this non-invasive treatment is, however, low.

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The Authors

A. W. S. Ritchie, MD, FRCSE, Senior Lecturer and Honorary Consultant Urological Surgeon.

N. J Parr, MD, FRCSE, Lecturer in Urology.

S. A. Moussa, FRCR, FRCSE, FRACS, Consultant Radiologist.

D. A Tolley, FRCS, Director and Consultant Urological Surgeon.

Requests for reprints to: A. W. S. Ritchie, The Scottish Lithotriptor Centre, Deaconess Hospital, 148 The Pleasance, Edinburgh EH8 9RS.

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Treatment of Caliceal Calculi

W. HUBNER and P. PORPACZY

Department of Urology, Policlinic Hospital, Vienna, Austria

Summary—We analysed the course of 80 "stone periods" (the time that elapses between making a diagnosis and passage of a stone, operation, or an out-patient's last check-up) in 62 patients with caliceal stones prior to the development of extracorporeal shockwave lithotripsy (ESWL) and endourology. The observation time per patient averaged 7.4 years; 16% of the stones passed spontaneously and 40% were removed surgically. The infection rate was 68% and 45% of the stones increased in size during the observation period. Retrospective evaluation showed that of 32 patients who underwent surgery, only 11 procedures were performed at the appropriate time. In the remaining 21 cases the timing of surgery was judged to have been too late because of the ensuing complications. In 8 patients stone growth led to staghorn calculi, 8 had acute obstruction with incipient urosepsis, 3 had chronic urinary infection and 1 had loss of kidney function.

We believe that 83% of all caliceal stones require intervention (ESWL or percutaneous nephrolithotomy) within 5 years of diagnosis. Only 11% of patients with caliceal calculi remain symptom-free after 10 years.

In the era of open stone surgery, physicians were reluctant to remove caliceal stones surgically because they were often asymptomatic and surgical removal required complicated techniques. Thus only calculi causing obstruction were removed surgically. With the introduction of ESWL and percutaneous litholapaxy, the treatment of caliceal calculi has been reassessed. The aim of this retrospective study was to determine the optimum timing for surgical treatment of caliceal stones so that guidelines can be established.

Patients and Methods

We analysed the course of 80 caliceal "stone periods" (*i.e.* the time between making a diagnosis and passage of a stone, operation, or an out-patient's last check-up) in 63 patients (mean age 57.3 years) between 1962 and 1983. The observation time per patient averaged 7.4 years and the average duration of a stone period was 4.9 years. Check-up consisted of case history, IVU and urine culture. Patients with obscure symptoms of accompanying urological pathology were excluded from the study.

Results

Primary caliceal stones were found in 49 patients, recurrent stones (following surgical extraction) in 18 and post-operative residual stones in 13; 70% of the calculi were found in the lower calices, 15% in the upper and 7.5% in the mid calices. Of the 80 caliceal stones, 6% were successfully removed by oral litholysis (uric acid calculus) and 16% passed spontaneously; 40% were removed surgically, the indications being pain, recurrent infections with or without stone growth, and haematuria; just under 40% were still *in situ* at the last follow-up (Fig.). In 68% of all cases symptoms of infection were found and in 45% the calculus had increased in size during the observation period; 51% of patients experienced pain and 23% reported a single episode or recurrent macrohaematuria. In 6 cases (7.5%) nephrectomy was performed after progressive growth resulting in staghorn stones. Five of these patients did not return for urological check-up.

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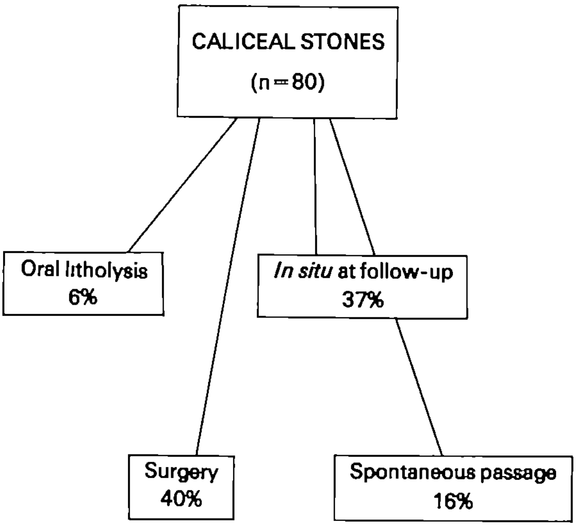

Fig. Follow-up of 80 caliceal stones before introduction of ESWL and endourology

To gain a better overall picture of the results, the patients were divided into 3 groups according to the duration of the stone period (2, 5 and 10 years respectively). Patients with stone periods exceeding 10 years were small in number and therefore excluded from the study (Table 1). During the first 2 years after diagnosis, 29% of stones passed spontaneously and 45% were removed surgically. In the 5-year group, only 13% of stones passed spontaneously and the infection rate was 69%. In the third group, more than 80% of the patients had significant infection and 78% showed signs of increasing stone size. Five out of 10 operations in this group were nephrectomies.

Retrospective Evaluation

As a result of our observations we have estimated when surgical intervention in these patients would have been appropriate.

Table 1 Follow-up of 72 Caliceal Stones

	Duration of stone period		
	1–2 years (n=31) (%)	*5 years (n=23) (%)*	*10 years (n=18) (%)*
Spontaneous passage	29	13	—
Surgical intervention	45	17	56
Infection	58	70	83
Stone growth	26	39	78
Free of symptoms	26	17	11

Conservatively treated patients

In the 2-year group, the conservatively treated patients experienced no major complications. In retrospect, therefore, none of these patients would have required further intervention at the time of open stone surgery (Table 2). We would now use ESWL/percutaneous nephrolithotomy (PCN) in 53% of these patients because of minor problems (moderate flank pain, infection).

In the 5-year group, 21% of the conservatively treated patients should have had surgical intervention. We would now use modern stone treatment (ESWL, PCN) in 79% of these patients. In the 10-year group, 38% should have undergone surgery at that time and another 38% would now be treated by ESWL/PCN. Only 13% of the stones passed spontaneously after more than 2 years and in the 5-year group the calculi did not pass spontaneously at all. Only 11% of patients with caliceal calculi remained problem-free after 10 years. In 7/48 cases, conservative treatment must be considered retrospectively as having been inappropriate; 27 patients in this group would today undergo ESWL/PCN.

Surgically treated patients

Retrospective evaluation revealed that of 32 patients who underwent surgery, only 11 interventions were performed at the right time. In the remaining 21 cases the timing of the operation was deemed too late because of the complications that arose (8 patients developed staghorn calculi, 8 had acute obstruction with incipient urosepsis, 3 had chronic urinary infection and 1 had loss of kidney function). In 6 elderly patients nephrectomy was required because of a non-functioning kidney or major stone mass.

Discussion

ESWL and endourological extraction of calculi have led to significant changes in stone therapy (Alken *et al.*, 1982; Alken, 1984; Chaussy and

Table 2 Retrospective Indication for Intervention (ESWL, PCN) in 27 Conservatively Treated Patients

	Indication for ESWL/PCN (%)	
Duration of stone period	*Then*	*Now*
2 years (n=17)	0	53
5 years (n=19)	21	79
10 years (n=8)	38	38

Schmiedt, 1983; Chaussy *et al.*, 1984; Clayman, 1984; Segura and LeRoy, 1984).

However, the decision as to when, how and where to remove a stone is not straightforward, since there are now many methods of treatment. Particularly controversial is the treatment of asymptomatic caliceal stones.

With the introduction of extracorporeal shock wave lithotripsy and percutaneous stone removal the belief that non-obstructive caliceal calculi should not be removed is no longer acceptable. Brannen *et al.* (1986), Mee *et al.* (1988) and Andersson and Sylven (1983) demonstrated that in the case of persistent, dull flank pain and non-obstructive caliceal stones, pain can be significantly reduced by removing the calculus. Mee *et al.* (1988) compared the relatively high cost of ESWL therapy with the cost of conservative treatment, including out-patients treatment, hospital admission, analgesia, diagnostic evaluation and days of missed work.

Approximately 5% of all caliceal stones can be treated by oral litholysis; a further 15% pass spontaneously.

Our findings suggest that 80% of caliceal stones require intervention within the first 5 years of diagnosis; after that time spontaneous passage is unlikely. Apart from the common indications such as pain, macrohaematuria and temperature, recurrent infections of the urinary tract and/or increasing stone size, flank pain of unknown origin is also an indication for intervention (Andersson and Sylven, 1983; Brannen *et al.*, 1986; Mee and Thuroff, 1988).

Completely asymptomatic, non-infected stones may safely remain untreated for a longer period of time. However, the significance of lithiasis must not be underestimated, for there is then a risk that patients will not attend for follow-up. They must be told that regular urological examination is necessary even if there is no recurrence of pain, so that any pathological changes can be detected early. In the case of severe infection of the urinary tract, which is mostly associated with stone growth, removal of the calculus should be performed without further conservative treatment.

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The Authors

W Hübner, MD, Urologist.
P. Porpaczy, MD, Head of Department of Urology.

Requests for reprints to. W. Hübner, Department of Urology, Policlinic Hospital, Mariannengasse 10, A-1090 Vienna, Austria

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Voiding Patterns and Prevalence of Incontinence in Women.
A Questionnaire Survey

P. SOMMER, T. BAUER, K. K. NIELSEN, E. S. KRISTENSEN, G. G. HERMANN, K. STEVEN and J. NORDLING

Department of Urology, Herlev Hospital, Herlev, Denmark

Summary—A detailed questionnaire on the occurrence of irritative and obstructive voiding symptoms, incontinence and the number of childbirths was sent out to 600 women aged between 20 and 79 years, randomly selected from the National Register; 432 (72%) returned the questionnaire and 414 (69%) were evaluable. The frequency of obstructive symptoms such as hesitancy, intermittency and decreased stream was low. Diurnal frequency with voiding intervals <3 h were recorded by more than 50% of the women and about 10% voided more frequently than every second hour. Nocturia increased significantly with age; 54 (13.6%) voided at least twice per night. About 40% complained of incontinence but this was troublesome in only 6%; 15.3, 13.3 and 11.5% had stress, urge and mixed incontinence respectively. More than 8% wore nappies or sanitary towels every day to protect against urinary leakage. Although the tendency to wear nappies or sanitary towels increased with age, the increase was not statistically significant. There was a positive correlation between the occurrence of stress incontinence and childbirth in the group as a whole.

Pathological voiding patterns and urinary incontinence in women have been described in selected groups: women seeking medical attention for voiding symptoms (Brooks *et al.*, 1983), women in selected age groups (Vetter *et al.*, 1981; Hørding *et al.*, 1986), women in the later stages of the menopause (Iosif and Bekassy, 1984), hospital patients, hospital staff etc. The prevalence of urinary incontinence in randomly selected groups of women ranges from 7 to 41% (Thomas *et al.*, 1980; Jolleys, 1988).

The purpose of this study was to determine the prevalence of stress, urge and mixed incontinence and to describe the normal voiding patterns in a randomly selected group of women aged 20 to 79 years.

Patients and Methods

A detailed questionnaire concerning irritative and obstructive voiding symptoms, urge and stress incontinence, the use of sanitary towels or nappies, past or present urogenital diseases, previous urogenital surgery, present drug treatment and deliveries was sent to 600 women aged between 20 and 79 years. They were selected randomly from the National Register and were divided into 6 decades with 100 women in each.

The obstructive symptoms comprised hesitancy, intermittency and decreased stream. The irritative symptoms included diurnal frequency, nocturia and urgency. The women were asked to keep a frequency chart for 3 days and nights on which they recorded the number of diurnal and nocturnal voidings.

The questionnaires were returned by 432 women (72%); 18 questionnaires were returned unanswered, so that 414 (69%) were evaluable; 44 women (7.3%) had previously had an operation for cystocele, prolapsus uteri or had undergone hysterectomy. Of these, 25 who still had urinary incontinence were excluded from the part of the investigation dealing with the correlation between childbirth and incontinence.

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The incontinence symptoms were divided into stress, urge and mixed incontinence, based on the questionnaires.

The Kruskall-Wallis analysis of variance, χ^2 test and Mann-Whitney unpaired rank sum test were used for statistical calculations and $P<0.05$ was considered statistically significant.

Results

Voiding patterns. Twenty-six women (6.3%) complained of hesitancy (Fig. 1A), but this occurred constantly in only 8 (1.9%). It was most frequent in the 2 youngest decades. Eighty-one women (19.6%) had intermittency (Fig. 1B) but this was constant in only 16 (3.9%). This symptom too was most frequent in the 2 youngest decades. Decreased stream was recorded by 83 women (20.1%), but only 2 complained of a constant weak stream. This symptom was most frequent in the second, third and sixth decades (Fig. 1C). Diurnal frequency (<3 h between each voiding) was recorded by 206 women (52.8%) (Fig. 1D); in 42 (10.8%) the intervals were less than 2 h. The frequency and severity of this symptom was evenly distributed throughout the decades. Nocturia $\geqslant 2$ times every night (Fig. 1E) was recorded by 54 women (13.6%) and 16 (4%) had nocturia 3 times or more. Both the frequency and the severity of this symptom increased significantly with age ($P<0.001$). Urgency was reported by 162 women (39.6%) (Fig. 1F) and 22 (5.4%) were troubled daily by this symptom.

Incontinence. The incontinence symptoms were divided into stress, urge and mixed incontinence. Incontinence of varying degrees was recorded by 160 women (40.1%) (Fig. 2); 61 (15.3%) had pure stress incontinence, 53 (13.3%) had pure urge incontinence and 46 (11.5%) had mixed incontinence. The incidence of women often or always troubled by incontinence was 0, 4.8, 4.6, 7.7, 9.2 and 8.1% in the second, third, fourth, fifth, sixth and seventh decades respectively. In addition, 1.3, 6.5, 4.6, 9, 13.2 and 12.9% of women in the second, third, fourth, fifth, sixth and seventh decades respectively always carried a sanitary towel or nappy as protection against urinary leakage. Statistical analysis showed no significant increase with age in the number of women who had to carry sanitary towels or nappies.

Correlation between childbirth and stress incontinence. Of 94 women who had not given birth, 11.7% had stress incontinence; of 308 who had given birth, 31.8% had stress incontinence. There was a significant positive correlation between birth and stress incontinence ($P<0.0005$) and between the number of births and the occurrence of stress incontinence ($P<0.001$). Excluding the 25 women who were incontinent despite incontinence surgery, there was still a positive correlation ($P<0.005$). These correlations held true when all of the decades were combined. Positive correlations were found in relation to births in the second and third decades, and for the number of births a positive correlation was noted only in the second decade.

The frequency chart kept for 3 days and nights showed that most women, independent of age, voided 5 to 7 times per day (mean 6.1) (Fig. 3A). The frequency of nocturia increased significantly with age ($P<0.001$), being most pronounced in the fifth, sixth and seventh decades (Fig. 3B).

Discussion

There have been few studies of voiding patterns in non-selected healthy women. This study showed that symptoms such as hesitancy, intermittency and weak stream were uncommon.

Voiding charts are often used to register voided volumes and voiding frequency. A frequency/volume chart for 48 h kept by a group of healthy women showed an average voiding frequency of 5.8/24 h. This was independent of age, but the incidence of nocturia increased with age (Larsson and Victor, 1988). We found a slightly higher diurnal frequency of 6.1 and a significant increase in nocturnal frequency with age ($P<0.0001$).

Diurnal frequency (or pollakiuria) is defined as micturition occurring more frequently than every third hour. The results of our questionnaire survey raise doubts about this definition. More than half of the women stated that they passed urine more frequently than every third hour. It would be more appropriate to define diurnal frequency as micturition occurring more frequently than every second hour, as was recorded by about 10% of women in the present study.

The frequency of nocturia is known to increase in older men. This has been attributed to a rise in the incidence of infravesical obstruction (prostatic hyperplasia) with age. Since this symptom also appears in older women, other factors such as age or increased nocturnal diuresis may be involved. The frequency of nocturia in older women was similar to that in men of the same age. Thus 23.4 and 28.3% of women in the present study, and 25.3 and 40.3% of men in a corresponding study (Sommer

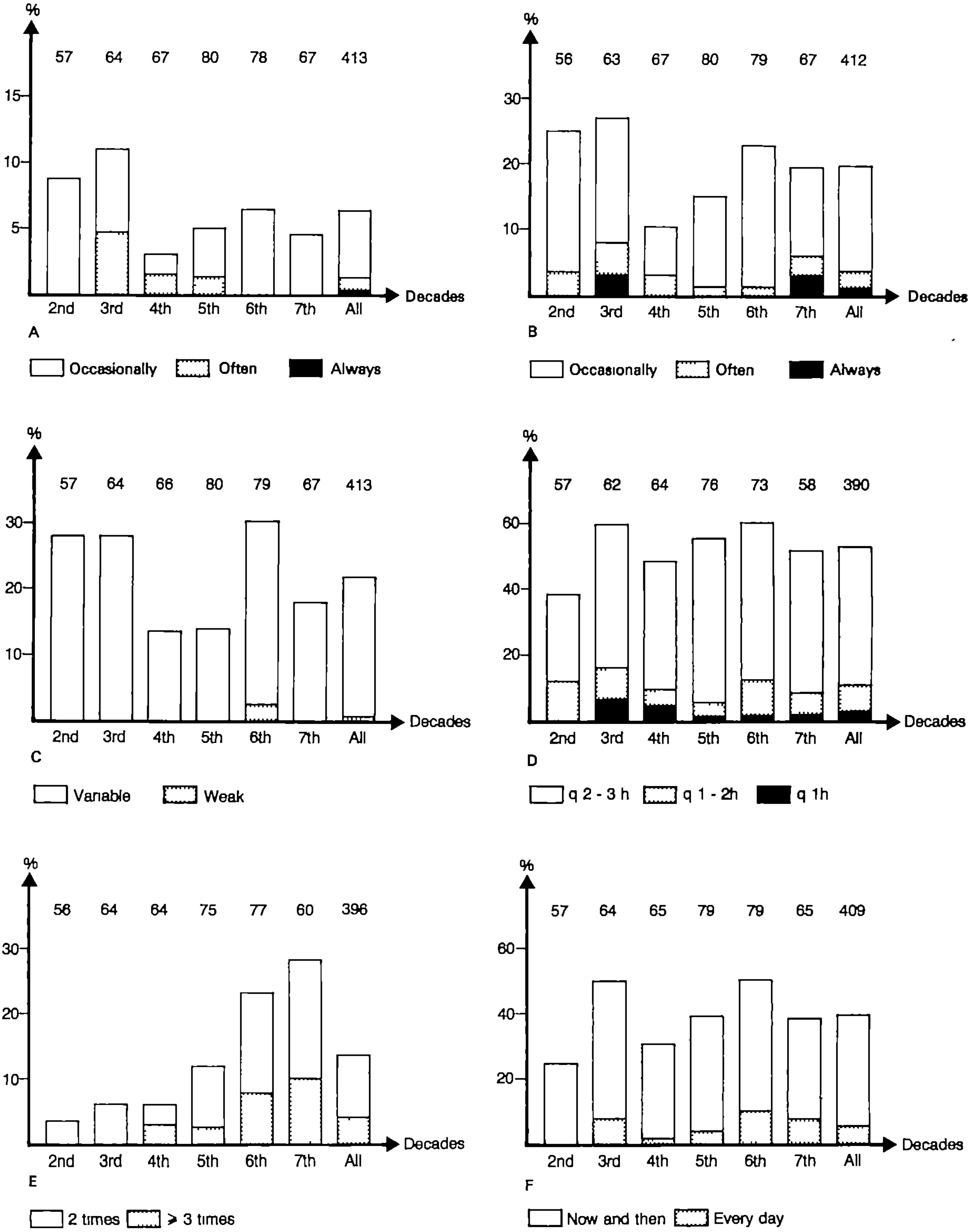

Fig. 1 Prevalence (in percentages) of voiding symptoms in the various decades. Figures above the columns indicate the number of questionnaires answered in each decade. (A) Hesitancy. (B) Intermittency. (C) Stream. (D) Diurnal frequency. (E) Nocturia. (F) Urgency

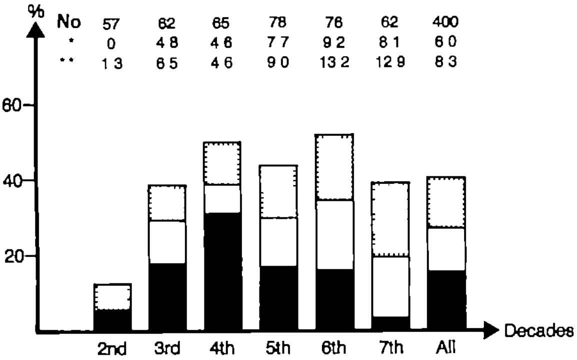

Fig. 2 Incontinence. *Percentage of women often or always troubled by incontinence **Percentage of women who always carried nappy or sanitary towel.
■ Stress incontinence. ☐ Mixed incontinence.
⬚ Urge incontinence

et al., 1990) in the sixth and seventh decades respectively had nocturia at least twice a night.

In accordance with Jolleys (1988), we found that approximately 40% of the women reported incontinence to a greater or lesser degree. Others have reported lower figures (Thomas *et al.*, 1980) but the differences are probably due to variations in definitions and questionnaires.

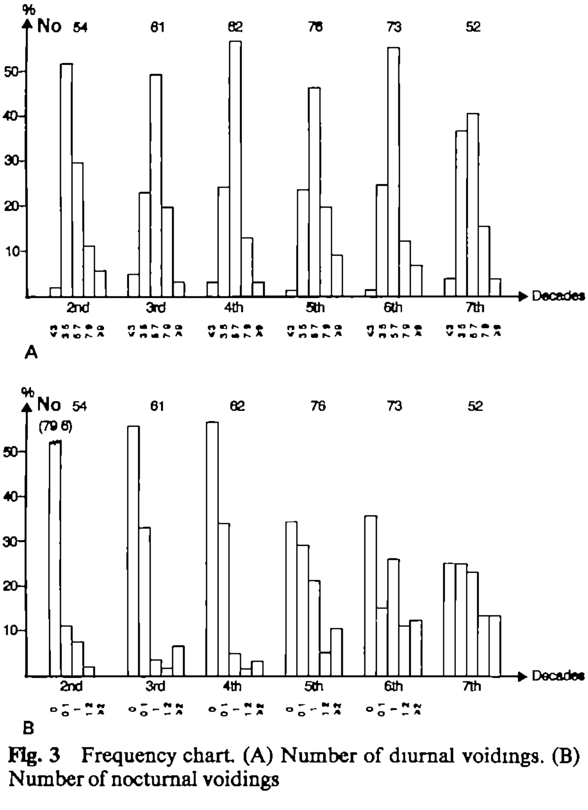

Fig. 3 Frequency chart. (A) Number of diurnal voidings. (B) Number of nocturnal voidings

Our finding of stress, urge and mixed incontinence in 15.3, 13.3 and 11.5% of women respectively was higher than that reported by Iosif and Bekassy (1984), who questioned a group of late menopausal women, but the distribution of the types of incontinence was similar.

When all of the age groups were combined, a significant positive correlation was found between stress incontinence and childbirth and also between stress incontinence and the number of births. This is in agreement with findings in other studies (Thomas *et al.*, 1980; Jolleys, 1988).

According to the type of incontinence, different forms of treatment are available, such as surgery, the administration of anticholinergic/calcium antagonistic drugs (Gerstenberg *et al.*, 1986) or pelvic floor exercises (Klarskov *et al.*, 1986). Further investigation into treatment for these troublesome symptoms is required.

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The Authors

P. Sommer, MD, Registrar
T Bauer, MD, Registrar
K. K Nielsen, MD, Registrar
E S Kristensen, MD, Registrar
G. G. Hermann, MD, Registrar.
K. Steven, PhD, Senior Registrar
J Nordling, PhD, Chief Urologist

Requests for reprints to: P Sommer, Mylius Erichsens Alle 60, DK-2900 Hellerup, Denmark.

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Visual Analogue Scales Distinguish between Low Urinary Flow Rates due to Impaired Detrusor Contractility and those due to Bladder Outflow Obstruction

J. McLOUGHLIN, P. D. ABEL, N. SHAIKH, J. WATERS and GORDON WILLIAMS

Department of Surgery, Royal Postgraduate Medical School, Hammersmith Hospital, London

Summary—In patients with symptoms suggestive of bladder outflow obstruction and a free flow rate < 12 ml/s a visual analogue scale was used to measure the response to the question "Compared to 5 years ago, how thick is your stream when you pass urine?". The visual analogue scale compared favourably with cystometry in distinguishing between low flow rates resulting from impaired detrusor contractility and low flow rates due to bladder outflow obstruction. A visual analogue scale may serve to alert the surgeon to the presence of impaired detrusor contractility and the need for a fuller urodynamic assessment in patients with a low urinary flow rate prior to consideration for prostatectomy.

Men with low urinary flow rates due to impaired detrusor contractility (IDC) who are treated by prostatectomy do less well than men with low flow rates due to bladder outflow obstruction (BOO) (Blaivas and Norlen, 1983). The distinction between these 2 groups cannot reliably be made on the basis of a flow rate alone (Axelrod *et al.*, 1986) and requires the use of cystometry, which is not always available. Patients with low flow rates due to IDC would be expected to have a poorer perception of their reduction in flow over a given period of time than patients developing BOO, whose symptoms are of more recent onset. It was on this basis that we studied the role of visual analogue scales for differentiating between these groups.

A visual analogue scale consists of a line drawn between 2 possible extremes to the response to a question. An individual may place a mark to reflect the degree to which the symptoms relate to the extremes. Visual analogue scales, while remaining subjective, have been used extensively in the past to gain more objectivity in that assessment. In urological practice, in conjunction with a careful history, they have been found to be more reliable than a history alone in distinguishing between stress and urge incontinence (Parkin and Davis, 1986).

Patients and Methods

Men presenting with symptoms suggestive of bladder outflow obstruction were assessed by means of a full history, physical examination and urinary flow rate assessment. Patients with a free flow rate < 12 ml/s on a voided volume > 200 ml were invited to undergo urodynamic assessment. On the day of attendance for cystometry the patient was asked to mark his response to the question "Compared to 5 years ago, how thick is your stream when you pass urine?" as an "X" along a 16-cm horizontal visual analogue scale. One end of the scale was marked "the same" and the other was marked "much thinner". The concept of the scale was explained to the patients and they were asked to mark an "X" along the scale in private. The point at which each patient placed his response was measured and the percentage of the total length of the scale was

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calculated to the nearest percentage and the result plotted on a scale (Fig.). Following a repeat free flow measurement the patient was catheterised and his residual urinary volume measured.

Cystometry was performed using a medium fill rate. At capacity the patient was invited to void with the pressure lines still in place. Following cystometry it was possible to distinguish 4 categories of patients. Bladder outflow obstruction was initially defined as a urethral resistance >0.6 (detrusor pressure at maximum flow/(maximum flow rate)^2) and then sub-classified according to maximum detrusor pressures at peak flow. Patients with a maximum detrusor pressure >45 cm H_2O in the presence of a peak flow rate <12 ml/s were termed "obstructed" (Blaivas and de la Rocha, 1985), whilst patients with a maximum detrusor pressure of 30 to 45 cm H_2O were classified as "indeterminate" (Blaivas, 1988). Patients with a maximum detrusor pressure of 30 cm H_2O associated with a flow rate of 12 ml/s or less were classified as "impaired detrusor contractility". A fourth category included patients with a residual volume >80 ml in the impaired detrusor contractility group who were considered to be "decompensated". The statistical significance of the results was analysed using the Mann Whitney test.

Results

Sixty-two men aged between 45 and 88 years (mean 64) were studied with cystometry and 43 were considered obstructed. The visual analogue scores in this group ranged from 45 to 91 (mean 75.8). Two patients had maximum detrusor pressures in the "indeterminate" range with visual analogue scores of 18 and 70 respectively. Thirteen had maximum voiding pressures <30 cm H_2O and 7 of these had IDC with visual analogue scores ranging from 5 to 56 (mean 22.7). Six patients were classified as decompensated with visual analogue scores ranging from 21 to 72 (mean 41). Residual volumes in this latter group ranged from 175 to 1100 ml on catheterisation. Patients with higher residual volumes tended to have higher scores on the visual analogue scale. Two patients who were found to be unobstructed (and unstable) had scores of 66 and 81 respectively. Two patients were unable to comply with instructions for completion of the scale.

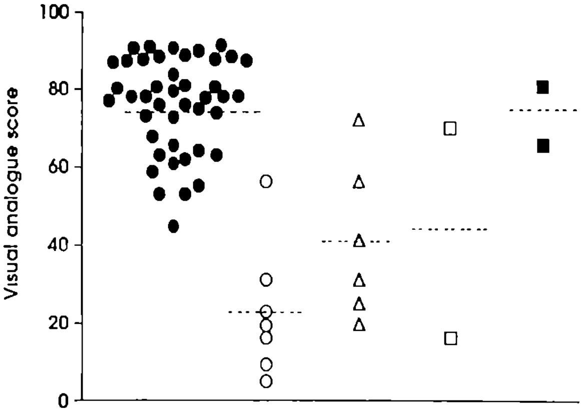

Fig. Visual analogue scores ●: obstructed ○· Impaired detrusor contractility. △. Decompensated. □. Indeterminate ■: Unobstructed.

Applying the Mann Whitney test, the mean values for the obstructed and the IDC groups were significantly different ($P<0.001$), as were those of the obstructed and the decompensated groups ($P<0.001$). The difference between the mean values of the decompensated and IDC groups was of borderline significance ($P<0.06$).

Discussion

The combination of obstructive symptoms and a low free flow rate has been suggested as a reliable indication for prostatectomy (Abrams, 1977). It has been shown, however, that a flow rate without pressure flow studies is insufficient to distinguish men with low flow resulting from bladder outflow obstruction from those with a low flow resulting from impaired detrusor contractility (Axelrod *et al.*, 1986). The response to prostatectomy in this latter group of patients is poor, so that management is difficult (Blaivas and Norlen, 1983; Blaivas and de la Rocha, 1985).

Blaivas (1988) defined impaired detrusor contractility as a maximum detrusor pressure on voiding of 30 cm H_2O with a corresponding flow rate of 12 ml/s or less. These patients have "obstructive" flow patterns. Studies analysing the characteristics of these flow rate patterns have failed to identify a reliable means of distinguishing between bladder outflow and IDC (Axelrod *et al.*, 1986). Without pressure flow studies, therefore, patients in the IDC group may be erroneously subjected to prostatectomy, even with a screening flow rate. We have avoided the use of the term "low pressure/low flow". In the original description of low pressure/low flow states, patients complained of conversional symptoms, and had intermittent flow rates and voiding pressures up to 65 cm H_2O (George and Slade, 1979; Barnes *et al.*, 1985). These patients are not comparable to the group considered in this study. We have chosen to use the definition of Blaivas (1988) to identify our IDC patients.

Two patients with symptoms suggestive of bladder outflow obstruction together with a low flow rate were found to be unstable but unobstructed on cystometric criteria. Symptoms are unreliable indicators of obstruction. Frequency and nocturia may be due to detrusor instability in the absence of obstruction (Turner Warwick *et al.*, 1973). Abrams and Feneley (1978) considered hesitancy to be a reliable indicator of obstruction but Blaivas (1988) described how hesitancy owing to an unstable contraction may be misinterpreted by the patient as having a full bladder. By the time the patient reaches the toilet the contraction has abated and his urge has gone, with the result that he then has to wait before he can void because his bladder contains only a small amount of urine (Blaivas, 1988). A low free flow rate in the absence of obstruction may be the result of overdistension of the patient's bladder prior to voiding; alternatively, it may be due to failure of the patient to relax when voiding, thus producing a non-representative flow of urine on any one occasion.

We have excluded patients with residual urinary volumes >80 ml from our IDC group so that poor urinary flow rates resulting from low bladder pressures due to detrusor decompensation, secondary to bladder outflow obstruction, could be distinguished from the IDC group. This volume is arbitrary but consistent with the description by Blaivas and Norlen (1983). Residual urinary volumes in patients with IDC have not been clearly defined. In the definition of IDC, it must be of value to include residual urinary volume as well as the pressure/flow relationship; otherwise patients with decompensated detrusor function, who may well benefit from outflow tract surgery, could be classified in the IDC group. Of the 6 patients in our study with residual volumes >80 ml, responses on the visual analogue scale increased approximately in relation to their residual volume (Fig.).

In this study we have demonstrated a statistically significant difference between the visual analogue scores of the obstructed and the IDC group. There is, however, some overlap of scores in these groups which reflects the subjectivity of this technique.

When used in combination with a screening free flow rate, a visual analogue scale may alert the urologist to the possibility of impaired detrusor contractility and lead him to seek further pressure/flow studies prior to prostatectomy. Further studies are in progress to assess the clinical value of this technique in situations where urodynamic facilities are not available.

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The Authors

J. McLoughlin, FRCS, Urological Registrar.

P. D. Abel, ChM, FRCS, Senior Lecturer and Honorary Consultant in Urology

N. Shaikh, FRCSE, Urological Registrar.

J. Waters, MLSO, Senior Technician.

Gordon Williams, MS, FRCS, Consultant Urologist.

Requests for reprints to: P. D. Abel, Department of Surgery, Hammersmith Hospital, Du Cane Road, London W12 0HS.

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Voiding Dysfunction due to Neurosyphilis

S. J. GARBER, T. J. CHRISTMAS and D. RICKARDS

Departments of Radiology and Urology, Middlesex Hospital, London

Summary—Three patients with neurosyphilis presenting with urinary frequency, incontinence and voiding dysfunction were investigated. Unlike the previously reported finding of areflexia in tabes dorsalis, all 3 had hypocompliant detrusor hyper-reflexia with detrusor-sphincter dyssynergia and post-micturition residual urine. One patient also had bladder neck dyssynergia treated by bladder neck incision. The other 2 patients were initially managed by intermittent catheterisation but 1 ultimately underwent urinary diversion. The clinical relevance of these findings and the treatment of this condition are discussed.

The incidence of syphilis has decreased over the last 50 years. This is largely due to penicillin, although increased awareness of the condition has prompted early diagnosis. Recently, however, there has been an increase in the number of new cases of syphilis, especially in homosexual men. Neurosyphilis, a late complication of the disease, is rare and few urologists have experience in the management of its lower urinary tract manifestations. It has been suggested that neurosyphilis causes hypocontractility or areflexia of the detrusor (Harper *et al.*, 1967; Erturk *et al.*, 1987), which may be stimulated to contract after administration of bethanechol (Wheeler *et al.*, 1986). We have investigated 3 patients with neurosyphilis and urinary symptoms.

Case Reports

Case 1. A 48-year-old homosexual man presented with urinary frequency, urgency, urge incontinence and nocturnal enuresis. He had a 5-year history of meningovascular syphilis, which had presented with loss of sensation below the waist and weakness in both legs. Most of his neurological signs had resolved since initial presentation but the urinary symptoms persisted. His lower limbs were hyper-reflexic with bilateral clonus and extensor plantar reflexes. He had a positive Romberg's sign. Examination was otherwise unremarkable. Laboratory investigations demonstrated a positive Treponemal haemagglutination test (TPHA) and negative HIV antibody titre. Videocystometrography (VCMG) revealed a hypocompliant bladder with superimposed phasic hyper-reflexic contractions and a maximum filling pressure of 43 cm H_2O. He was continent throughout the filling phase and his bladder capacity was 350 ml. He voided at a maximum flow rate of 12 ml/s, a maximum detrusor pressure of 82 cm H_2O and mean voiding detrusor pressure of 68 cm H_2O. On screening during voiding he was noted to have impaired relaxation of the distal sphincter mechanism and there was also evidence of bladder neck dyssynergia in the form of a positive "Whiteside trapping sign". The volume of post-micturition residual urine was 100 ml. He was treated by bladder neck incision.

Case 2. A 71-year-old man presented with recurrent urinary tract infections, urinary frequency, urgency, urge incontinence and a decreased stream. He had a 35-year history of neurosyphilis with features of both general paralysis of the insane (GPI) and tabes dorsalis. He had anaesthesia and weakness in both legs and a typical stamping tabetic gait. VCMG demonstrated a hypocompliant bladder with a maximum filling detrusor pressure of 96 cm H_2O and incontinence towards the end of filling. On screening the bladder was trabeculated, with a "fir tree" appearance (Fig 1), and the total capacity was 1500 ml. He voided with a maximum flow rate of 14 ml/s, maximum voiding detrusor pressure of 110 cm H_2O and mean voiding detrusor pressure of 85 cm H_2O. During voiding the bladder neck and prostatic urethra were wide open with a "spinning top" appearance (Fig. 1) and outflow obstruction appeared to be at the level of the distal sphincter mechanism. He voided a total of 700 ml with considerable abdominal straining and is currently managed by intermittent catheterisation.

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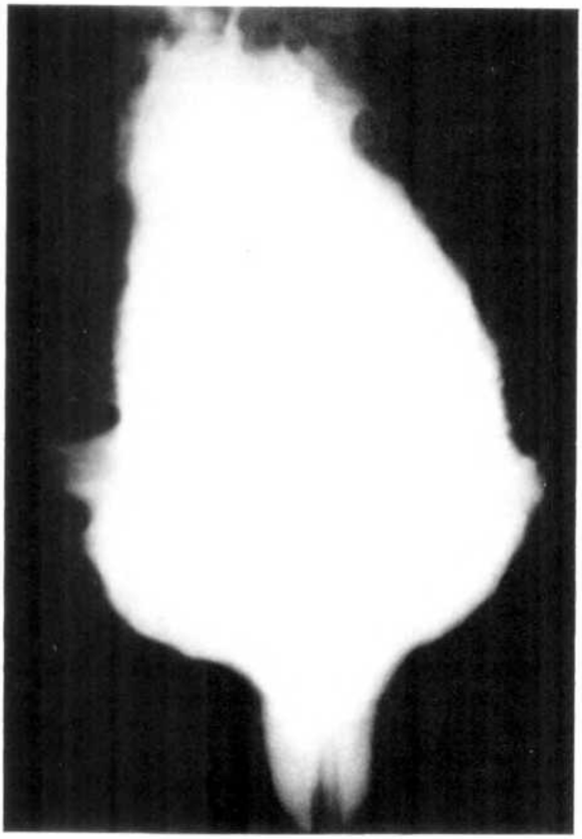

Fig. 1 Urodynamic tracing from Case 3 showing hypocompliance with superimposed phasic hyper-reflexia during filling. The patient voids with high detrusor pressure and low flow due to detrusor-sphincter dyssynergia.

Case 3. A 73-year-old woman presented with recurrent urinary tract infections, urinary frequency and incontinence. She had a long history of impaired hearing, optic atrophy and leg weakness secondary to neurosyphilis. She had a positive TPHA test. VCMG showed a hypocompliant rise in pressure with superimposed phasic detrusor hyper-reflexia leading to incontinence at a pressure of 55 cm H_2O. The total bladder capacity was 350 ml. She voided with abdominal straining but achieved a maximum flow rate of only 15 ml/s with a maximum detrusor pressure of 71 cm H_2O (Fig. 2). Post-micturition residual urine amounted to 50 ml. During fluoroscopy the distal sphincter did not appear to relax adequately during attempted voiding. She underwent a Bramble clam enterocystoplasty (Bramble, 1982) and urethral dilatation. After this she had difficulty in voiding, was found to have a large volume of residual urine and developed recurrent urinary tract infections. Intermittent self-catheterisation (ISC) was performed thrice daily but the infections persisted. She ultimately underwent urinary diversion after 4 months with an indwelling urethral catheter.

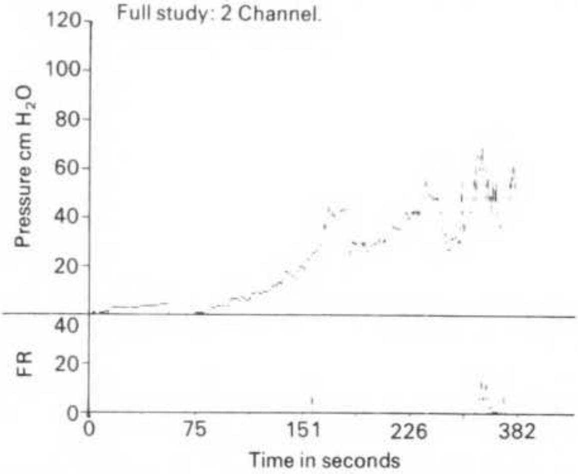

Fig. 2 Voiding cystogram in Case 2 showing a "fir tree" bladder, wide open prostatic urethra and the verumontanum.

Discussion

Meningo-vascular syphilis causes endarteritis obliterans leading to arterial thrombosis in any part of the central or peripheral nervous system. Intracranial disease may clinically resemble a cerebrovascular accident with upper motor neurone (UMN) signs. Lower motor neurone (LMN) signs are found with lesions affecting the spinal cord.

GPI produces an insidious dementia with concomitant UMN signs which are usually bilateral and initially mild. In tabes dorsalis, joint position sense is impaired and a stamping gait is seen. Absence of visceral sensation may result in bladder overfilling, the so-called tabetic bladder (Brain, 1978). These are the commoner clinical syndromes, but any combination of these can occur, the symptoms and signs depending on which predominates. Bladder dysfunction secondary to neurosyphilis is well recognised. Detrusor areflexia and decreased bladder sensation, leading to bladder overdistension, have been reported, mostly in patients with tabes (Brodie *et al.*, 1940; Wheeler *et al.*, 1986; Erturk *et al.*, 1987). A single case out of 13 had detrusor hyper-reflexia (Brodie *et al.*, 1940).

We have described 3 patients with neurosyphilis presenting with urinary frequency and incontinence as well as voiding difficulty. In all cases VCMG demonstrated a hypocompliant form of detrusor hyper-reflexia leading to incontinence in 2. Voiding dysfunction due to detrusor-sphincter dyssynergia and post-micturition residual urine have also been shown. The urodynamic characteristics of these 3 patients suggested that UMN neurosyphilitic involvement was responsible for the voiding dysfunction. All had a mixed form of neurosyphilis rather than tabes dorsalis in isolation and this might account for the presence of detrusor hyper-reflexia and dyssynergia as opposed to detrusor areflexia.

The management of these patients is difficult. Pharmacotherapy can partially inhibit detrusor hyper-reflexia but may decrease voiding efficiency and hence increase post-micturition residual urine. Intermittent catheterisation will allow adequate drainage and delay the onset of hyper-reflexia. The patient in this series who underwent a clam enterocystoplasty was unable to void adequately because of sphincter dyssynergia and had to perform ISC, which she found difficult due to impaired vision. Unfortunately, some patients with neurosyphilis are not able to perform ISC because of deterioration in mental function or impaired manual dexterity.

This study demonstrates the importance of VCMG in the assessment of voiding disorders in patients with neurosyphilis. Bladder dysfunction may vary from complete detrusor areflexia to detrusor hyper-reflexia and sphincter dyssynergia.

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The Authors

S. J. Garber, MRCP, Registrar in Radiology
T. J. Christmas, FRCS, Research Fellow in Urology
D. Rickards, FRCR, Consultant Radiologist.

Requests for reprints to D. Rickards, Department of Radiology, Middlesex Hospital, Mortimer Street, London W1N 8AA

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Clinical Significance of the Antibody-coated Bacteria Test in Patients with Candiduria

M. OHKAWA, S. TOKUNAGA, R. SHODA and H. HISAZUMI

Department of Urology, Kanazawa University, Kanazawa, Japan

Summary—The clinical significance of the antibody-coated bacteria (ACB) test was evaluated with urine from 20 patients with candiduria. The relationship between the *in vitro* antibody-coating test for *Candida albicans*, urinary immunoglobulin (Ig) levels and serum antibody titres was evaluated in 40 patients without candiduria, 23 of whom had bacterial urinary tract infection (UTI). Urine specimens from 19 of the 20 patients with candiduria gave a positive result regardless of clinical symptoms; 12/23 specimens of urine from patients with bacterial UTI were positive for antibody-coated *C. albicans* cells, but there were no positive samples in the patients without UTI. All of the coating-positive patients had serum antibody titres $\geqslant 1:160$, the class of antibody being dependent on the urinary Ig levels.

The ACB test for candiduria is of little clinical value in indicating invasive *Candida* UTI as the *Candida* cells appear to adhere to antibodies in urine contaminated with circulating fluids.

Since the introduction of antimicrobial, immunosuppressive and antineoplastic agents, the frequency with which *Candida* species are isolated from urine has increased dramatically (Roy *et al.*, 1984). There are, however, no universally accepted diagnostic criteria, and it is not known whether the presence of candiduria signifies benign saprophytic colonisation or true infection of the urinary tract.

Following the pioneering works of Thomas *et al.* (1974) and Jones *et al.* (1974), who suggested that an antibody-coated bacteria test could be useful in distinguishing kidney infection from bladder infection, the test has been applied to urine samples in order to demonstrate kidney and/or bladder infection with tissue invasion (Kwasnik *et al.*, 1979; Hulter *et al.*, 1984). On the other hand, there have been reports that the ACB test for urine has little clinical value (Schardijn *et al.*, 1984; Greenberg *et al.*, 1986).

The purpose of the present study was to determine whether the ACB test for candiduria could be used to indicate true infection of the urinary tract.

Patients and Methods

Twenty patients (15 males and 5 females; mean age 66.3 years) with candiduria ($\geqslant 10^4$ cfu/ml) submitted urine samples for ACB testing. The species isolated from the specimens were *Candida albicans* in 19 patients and *Candida tropicalis* in 1. All patients had underlying diseases of the urinary tract, such as neurogenic bladder, bladder cancer or prostatic hyperplasia. Indwelling urinary catheters were present in 15 patients (75%) and all had received antibiotics before the study.

For the *in vitro* antibody coating test and the measurement of immunoglobulin (Ig) levels in the urine, urine and blood samples were obtained simultaneously from 23 patients with urinary tract infection due to bacteria and 17 patients without UTI. All of the patients with bacterial UTI (14 males and 9 females; mean age of 69.3 years) had underlying conditions similar to those of the patients with candiduria; 13 patients (57%) were managed by indwelling urinary catheters and 19 (83%) had been treated with antibiotics before the study. Of the patients without UTI (16 males and 1 female; mean age of 53.1 years), 11 had urological

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disease (*e.g.* prostatic hyperplasia) and 6 had glomerular diseases (*e.g.* glomerulonephritis). Proteinuria was detected in all patients with glomerular disease but in none of those with urological disease.

Antibody titre against *C. albicans* in the serum was determined in all 60 patients.

Detection of ACB. The ACB test was performed according to a modification of the method of Thomas *et al.* (1974). The urine sediment was washed with 0.01 M phosphate buffered saline (PBS), pH 7.3; 0.2 ml of 1:5 dilution of fluorescein-conjugated antihuman globulin of goat origin (Medical & Biological Laboratories Co., Nagoya, Japan) was then added and incubated at 37°C for 30 min. Smears were prepared and observed using the XF-EFD fluorescence microscope (Nikon Co., Tokyo, Japan).

Fluorescein-conjugated monospecific antisera of goat origin against human IgG, IgA and IgM (Medical & Biological Laboratories Co., Nagoya, Japan) were used to determine the class of antibody in the immunofluorescence-positive specimens.

In vitro antibody coating. Urine specimens were centrifuged and the supernatant obtained. *C. albicans* ATCC 10259 strain was grown in Sabouraud's broth at 30°C for 24 h, cells were harvested, washed twice with PBS and resuspended in PBS to a final concentration of approximately 10^8 cfu/ml. The supernatant (0.9 ml) was then added to 0.1 ml of the cell suspension, while 0.9 ml of the serum obtained by centrifugation of the blood specimen was also added to 0.1 ml of the suspension. Both were mixed and incubated at 37°C for 30 min. The ACB test was carried out as described above.

Determination of the class of antibody in the coating-positive urine and serum specimens was performed, using the fluorescein-conjugated monospecific antisera.

Measurement of Ig levels in the urine. IgG, IgA and IgM levels in the urine were quantified by the single radial immunodiffusion method using immunodiffusion plates (Partigen; Behringwerke AG, Marburg, FRG). The measurements were performed using samples of supernatant from the urine samples used for the *in vitro* antibody coating test.

Detection of antibodies against Candida species. Antibody titre against *Candida* species in the serum was measured by the indirect haemagglutination test, using formalinised and lyophilised sheep erythrocytes coated with or without the *C. albicans* cell wall antigens (Hoffman-La Roche, Basel, Switzerland).

Results

Urine specimens from 19 of the 20 patients with candiduria were coating-positive; only 1 patient with a coating-negative urine specimen from which *C. albicans* was isolated had a serum antibody titre of 1:160 and no proteinuria. Of 19 fluorescence-positive specimens, fluorescence was positive for IgG in all, for IgA in 17 and for IgM in 9 specimens.

Table 1 describes the results of the *in vitro* antibody coating test of the urine specimens. The cells of the *C. albicans* strain were coated with antibody in 12/23 urine specimens from the patients with bacterial UTI but not in the specimens from patients without UTI. The classes of antibodies in the coating-positive specimens (Fig. 1) were similar to those in the coating-positive specimens of the patients with candiduria. Urinary Ig levels in relation to the results of *in vitro* coating tests are shown in Figure 2. The concentrations of IgG, IgA and IgM in the coating-positive specimens were significantly greater than those for Igs in the coating-negative ones ($P<0.01$ for IgG, <0.05 for IgA and <0.01 for IgM by Welch's t test). Proteinuria was detected in all of the coating-positive specimens.

The *C. albicans* cells were coated *in vitro* with antibody in all of the 40 serum specimens; the coating tests were positive for IgG in all, for IgA in 35 and for IgM in 18 specimens.

Serum reciprocal antibody titres against the cell wall antigens of *C. albicans* according to the patient groups are shown in Table 2. The titres considered normal ($\leqslant 1:160$) (Müller, 1976) were detected in 13/17 patients without UTI, in 10/20 candiduria patients and in 9/23 bacterial UTI patients; there was a significant difference between the patients with bacterial UTI and those without UTI ($P<0.05$ by Fisher's exact probability test). The patients

Table 1 Results of *in vitro* Antibody Coating Tests for Urine and the Classes of Antibodies in the Coating-positive Specimens

	No. of coating-positive patients (%)	*Class of antibody*		
		IgG	*IgA*	*IgM*
Patients with bacterial UTI (n=23)	12 (51.2%)	12	11	6
Patients without UTI (n=17)	0			

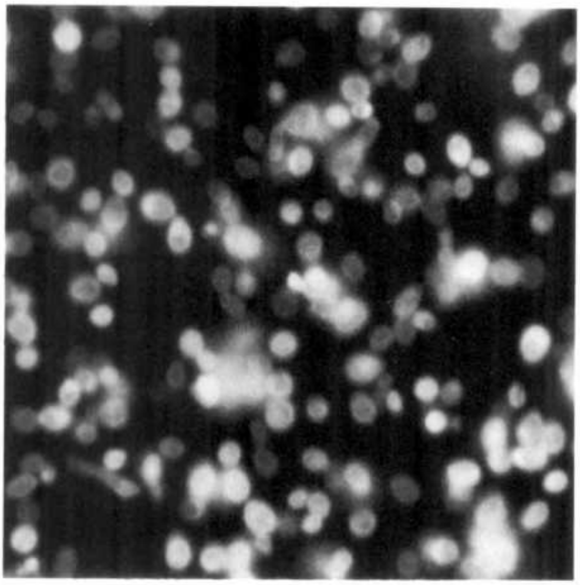

Fig. 1 A representative positive test of *in vitro* antibody coating for urine, using *C. albicans* ATCC 10259 strain and fluorescein-conjugated monospecific antiserum against human IgA (× 400).

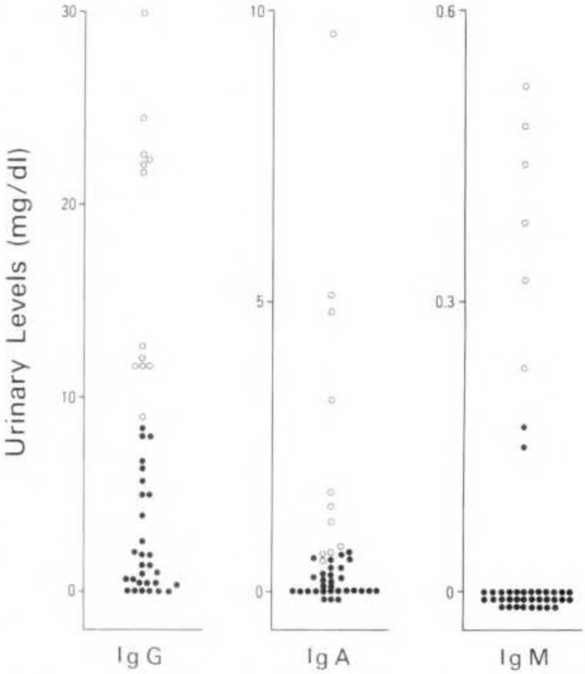

Fig. 2 Urinary IgG, IgA, and IgM levels in relation to results of *in vitro* antibody coating tests. ○: positive test; ●: negative test.

exhibiting *in vitro* coating-positive urine tests had titres of ⩾1:160.

Discussion

There have been many reports concerning the ACB test for urine and its ability to indicate bacterial invasive UTI (Thomas and Forland, 1982), but very few reports on the ACB test for *Candida* species (Everett *et al.*, 1975; Braude and Block, 1977). We performed the ACB test on urine from candiduria patients in order to evaluate the ACB test as a diagnostic aid. Although there is controversy regarding the criteria for *Candida* colony counts in *Candida* UTI, we selected patients with ⩾10^4 cfu/ml of *Candida* species in urine based on previous reports (Kozinn *et al.*, 1978; Goldberg *et al.*, 1979); all of the isolates except for 1 strain of *C. tropicalis*, were *C. albicans*.

Antibody-coated *Candida* cells were detected in almost all patients with candiduria regardless of the presence or absence of clinical symptoms (including fever and flank pain); more than half of the coating-positive patients had temperatures less than 37°C and no flank or lower abdominal pain when the specimens were collected. These findings are similar to those reported by Everett *et al.* (1975), but the reasons for the frequent occurrence of coating-positive *Candida* cells have not yet been defined.

Thomas *et al.* (1978) showed by indirect immu-

Table 2 Distribution of Serum Reciprocal Antibody Titres against *Candida albicans* Measured by Indirect Haemagglutination Test

	No. of patients with the following titres:										
	<10	*10*	*20*	*40*	*80*	*160*	*320*	*640*	*1280*	*2560*	*>5120*
Patients with candiduria (n = 20)	0	0	0	0	5	5	3	4	1	2	0
Patients with bacterial UTI (n = 23)	0	0	0	1	2	6	6	6	2	0	0
Patients without UTI (n = 17)	0	3	3	1	3	3	4	0	0	0	0

nofluorescence that a free, antibacterial antibody in the urine of patients with UTI might react with bacteria. Based on 1 instance involving the *in vitro* coating test against *C. albicans*, Braude and Block (1977) suggested that fungi contaminating the urine of uninfected patients with proteinuria might become coated with antibody, thus constituting a source of false-positive results. In the present study, proteinuria was detected in 9/19 coating-positive patients but not in the 1 coating-negative patient, findings which support the speculation of Braude and Block (1977). To investigate this possibility, we performed the *in vitro* antibody-coating test against *C. albicans*, using urine and serum from patients without candiduria, in relation to urinary Ig levels and the serum antibody titres. For the *in vitro* test, patients with bacterial UTI were selected whose background factors were similar to those of the candiduria patients. Patients without UTI, including those with proteinuria due to glomerular disease, were also examined. Antibody-coated *C. albicans* cells were observed *in vitro* in more than half of the specimens from the patients with bacterial UTI. The results of the classes of antibodies in the coating-positive patients were dependent on the urinary Ig levels. Patients with proteinuria due to glomerular disease had low urinary Ig levels; the specimens from these patients showed negative *in vitro* antibody coating.

Since almost everyone encounters *Candida* species because of their saprophytic nature, antibodies to the organisms are always present in the sera of humans, including healthy men (Müller, 1976). In the present study, serum antibodies were detected in all 60 patients, although the titres varied widely. The distribution pattern of the serum titres in the candiduria patients was similar to that in the bacterial UTI patients, probably due to the similar background factors. The titres in the bacteria UTI patients were greater than those in the patients without UTI; all of the *in vitro* coating-positive patients had titres $\geqslant 1:160$. The positive results of the *in vitro* coating test for all of the serum specimens support the haemagglutination test data that all subjects had antibodies against *Candida* species in their serum, and suggest that the serum antibodies easily combine with *Candida* cells. In addition, the classes of antibodies in the candiduria patients were similar to those in the *in vitro* coating-positive serum and urine specimens. Based on these results, it was thought that the antibodies detected in the urine of patients without candiduria and with bacterial UTI might originate mainly in inflow of body fluids, including blood, due to tissue injuries by the UTI. It is also reasonable to presume that the positive ACB tests for candiduria are partly due to passage of the circulating antibodies against *Candida* species into the urine.

Since the present study strongly suggests that *Candida* cells combine easily with the antibodies in urine contaminated with circulating body fluids, the ACB test for candiduria is of little value in distinguishing invasive *Candida* UTI from benign saprophytic colonisation.

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The Authors

M. Ohkawa, MD, Associate Professor
S. Tokunaga, MD, Lecturer.
R. Shoda, MD, Clinical Associate
H. Hisazumi, MD, Professor and Chairman

Requests for reprints to: M. Ohkawa, Department of Urology, School of Medicine, Kanazawa University, Takaramachi 13-1, Kanazawa 920, Japan

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Acceleration of Flow Rate in Obstructive Detrusor Instability

A. CUCCHI

Department of Urology, Policlinico S Matteo, Pavia, Italy

Summary—The acceleration of flow rate ($\bar{a}$) was calculated from spontaneous free flow uroflowmetry in 86 males with bladder outflow obstruction due to benign prostatic hypertrophy. Forty patients had stable bladders and 46 had detrusor instability. The parameter $\bar{a}$ was also determined in 30 controls.

All of the obstructed patients had lower values of $\bar{a}$ than the controls but patients with detrusor instability tended to show a higher acceleration of flow rate than those with stable bladders. In individual cases, however, parameter $\bar{a}$ was unreliable in distinguishing stable from unstable patients.

Acceleration of flow rate is a simple urodynamic parameter which reflects the velocity of opening of the vesical neck. It can be easily derived from standard free flow uroflowmetry and does not vary according to the volume of urine voided (Susset, 1983). Kadow and Abrams (1987) proved that such a parameter is impaired in obstructed men in the "prostatic" age group—which accords with the contraction velocity of the detrusor muscle (and thereby with the speed of vesical neck opening) being affected in prostatic obstruction (Griffiths, 1977; Susset, 1983).

The aim of the present study was to investigate the acceleration of flow rate in proximally obstructed males, with particular emphasis on the differences between stable and unstable bladders.

Patients and Methods

Patients with prostatism are usually assessed at this unit by spontaneous free flow uroflowmetry and medium-fill water cystometry with pressure flow studies. Urine flow rate is measured by a weight transducer. Cystometry is performed by infusing 0.9% saline at room temperature through a 10F Nélaton transurethral catheter. Abdominal pressure (p_{abd}) is measured through a 16F rectal balloon catheter inflated with 10 ml saline; detrusor pressure (p_{det}) is recorded using an 8F Nélaton transurethral catheter by electronically subtracting p_{abd} from intravesical pressure (p_{ves}). During filling, care is taken to note detrusor instability (DI) as defined by phasic, involuntary detrusor contractions (Abrams *et al.*, 1988). At maximum cystometric capacity the 10F catheter is removed and a pressure flow study is done with the patient upright. Detrusor and abdominal pressures and the urine flow rate are recorded on a paper strip chart recorder.

From the patients referred with prostatism between 1987 and 1989 a selection was made of those who had clinically proven benign prostatic hypertrophy (BPH) and who also showed a clinical and urodynamic pattern of bladder outflow obstruction (BOO). The latter was defined by pressure flow study as a detrusor pressure at maximum flow (p_{det} Q_{max}) of >75 cm H_2O. BPH patients with high maximum flow rates (Q_{max}) at spontaneous free flow uroflowmetry (>15 ml/s) were considered urodynamically obstructed (high flow BOO) if, in addition to a p_{det} Q_{max} >75 cm H_2O, they showed a maximum detrusor pressure ($p_{det\ max}$) in excess of 100 cm H_2O (Smith, 1968). Patients receiving treatment with drugs that could interfere with detrusor function were excluded, together with those who, in addition to BPH, had urethral

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strictures, bladder stones or neoplasms, neurological, metabolic or mental abnormalities or any other diseases that could directly or indirectly affect bladder filling and/or voiding. Those with positive urine cultures were also excluded.

A total of 86 patients with BPH met the criteria. Of them, 40 (mean age 60 ± 9 years) had stable bladders (Group B) and 46 (mean age 66 ± 8 years) had DI (Group A). For each subject in the 2 groups, the acceleration of flow rate ($\bar{a}$, in ml/s^2) was calculated from spontaneous free flow uroflowmetry as the ratio of maximum flow rate divided by the time (in s) to Q_{max} (Susset, 1983). In addition, the opening pressure ($p_{det\ op}$, in cm H_2O) was determined in each patient from a pressure flow study (with a correction of 1 s due to the time needed for the urine to pass through the urethra and reach the flowmeter). Such a parameter appears to approximate closely to the pressure needed to open the urethral lumen and keep it open in order to ensure urine flow. Thus, it is taken as a good estimate of the degree of obstruction of the vesical outlet, at least in those types of proximal urethral obstruction, as in BPH, which are defined as mostly "compressive", *i.e.* characterized just by an increased opening pressure (Schaefer *et al.*, 1988).

A group of 30 males (mean age 62 ± 7 years) referred with recurrent infections of the lower urinary tract acted as controls (Group C). At the time of the examination, no-one in this group showed pathological findings at cystoscopy, or intravenous urography or transrectal sonography and there were no signs of urinary infection. Uroflowmetry, cystometry and pressure flow studies revealed no abnormalities. These patients had no neurological, metabolic or mental diseases and were not receiving treatment with drugs that might affect detrusor function.

Table 1 shows the median and range of the following parameters, calculated for Groups A and B and for the controls from spontaneous free flow uroflowmetry: volume voided (V_{void}, in ml); total bladder volume (V_{tot}, in ml), *i.e.* V_{void} + residual urine as measured by catheterization; Q_{max} (in ml/s); corrected maximum flow rate (cQ_{max}, per s), *i.e.* Q_{max} divided by the square root of V_{tot} (von Garrelts, 1957), which is a volume-independent measure of the urinary flow; $\bar{a}$ (in ml/s^2). The opening pressure ($p_{det\ op}$, in cm H_2O) is also shown in Table 1.

Differences among the 3 groups were checked for statistical significance by a method suitable for non-parametric data, *i.e.* by Dunn's multiple-comparison procedure following a Kruskal-Wallis test. Wilcoxon's rank sum and Student's *t* tests were used to check the significance of differences in the acceleration of flow rate (and, respectively, in the subjects' mean ages) between the 86 obstructed patients as a whole (Groups A and B) and the 30 controls in Group C. Student's *t* test was also used to check the significance of differences in the patients' mean ages between Groups A and B.

Methods, definitions and units conform to the standards proposed by the International Continence Society (Abrams *et al.*, 1988) except where specifically noted.

Results

The patients' mean ages did not differ significantly in the obstructed patients as a whole (63 ± 9 years) and in the controls (62 ± 7), but were higher ($P < 0.005$) in Group A (66 ± 8) than in Group B (60 ± 9).

Medians and ranges of various parameters are reported in Table 1. No significant differences were found among the 3 groups with regard to the volume voided (V_{void}) and the total bladder volume (V_{tot}). The peak flow rate (Q_{max}) and the corrected peak flow (cQ_{max}) were higher ($P < 0.001$) in the controls than in the other 2 groups. Neither of these parameters differed significantly between Groups A and B.

With regard to $\bar{a}$, it was significantly higher in the controls than in the 86 obstructed patients as a whole (Table 2). The same parameter was higher ($P < 0.001$) in Group C than in the other 2 groups and lower in Group B than in Group A ($P < 0.01$).

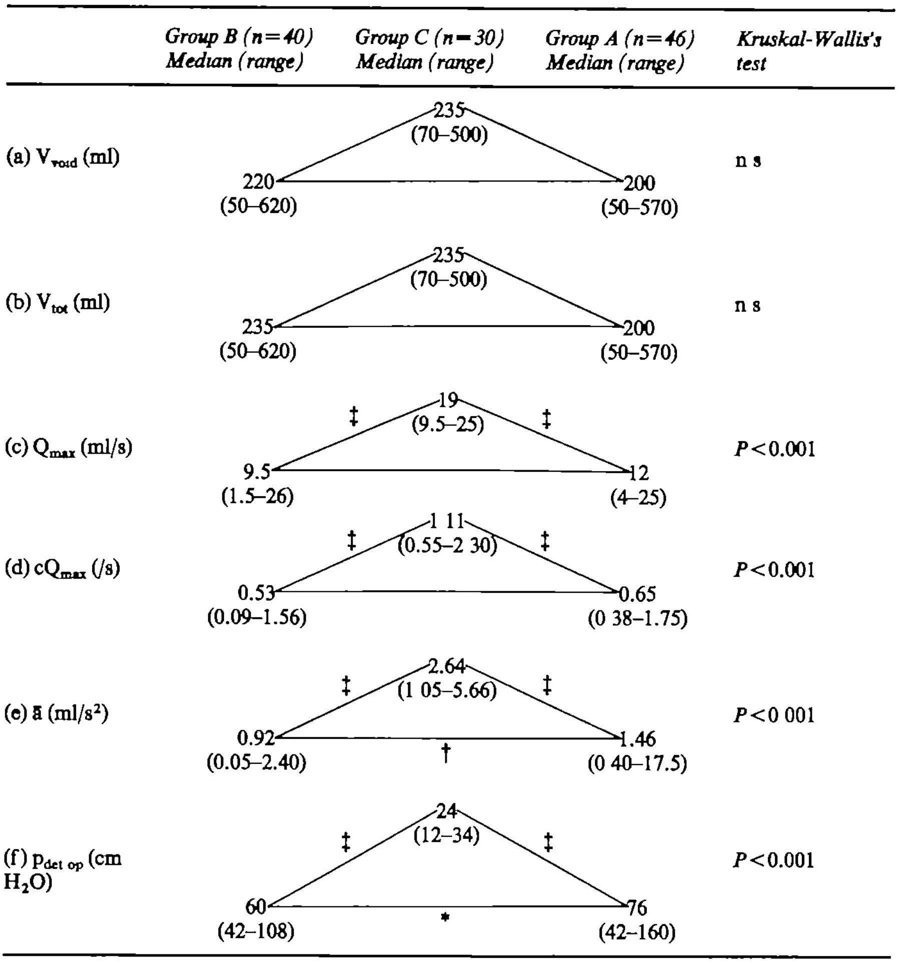
The opening pressure ($p_{det\ op}$) was higher in Group A than in Group B ($P < 0.05$) and lower in the controls than in Groups A ($P < 0.001$) and B ($P < 0.001$).

Discussion

The patients' mean ages were significantly higher in the group with obstructive detrusor instability (ODI), which accords with the statement of Abrams (1985) that DI is strictly related to age. It must be noted, however, that the opening pressure too was higher in the group with DI (Table 1, f). This is consistent with the finding that in proximally obstructed bladders, as in BPH, DI relates to the degree of obstruction of the vesical outlet (Cucchi, 1988).

The present results also showed that the acceleration of flow rate tended to be lower in the obstructed patients than in the controls (Table 2),

Table 1 Medians, Ranges and Significance Levels of Difference (Kruskal-Wallis's test and Dunn's multiple-comparison procedure) for various parameters in Groups A (unstable), B (stable) and C (controls)



	Group B (n=40) Median (range)	*Group C (n=30) Median (range)*	*Group A (n=46) Median (range)*	*Kruskal-Wallis's test*
(a) V_{void} (ml)	220 (50–620)	235 (70–500)	200 (50–570)	n s
(b) V_{tot} (ml)	235 (50–620)	235 (70–500)	200 (50–570)	n s
(c) Q_{max} (ml/s)	9.5 (1.5–26)	19 (9.5–25)	12 (4–25)	$P<0.001$
(d) cQ_{max} (/s)	0.53 (0.09–1.56)	1 11 (0.55–2 30)	0.65 (0 38–1.75)	$P<0.001$
(e) $\bar{a}$ (ml/s^2)	0.92 (0.05–2.40)	2.64 (1 05–5.66)	1.46 (0 40–17.5)	$P<0$ 001
(f) $p_{det\ op}$ (cm H_2O)	60 (42–108)	24 (12–34)	76 (42–160)	$P<0.001$

Dunn's multiple-comparison procedure: * $P<0.05$; † $P<0.01$, ‡ $P<0.001$.

which confirms similar findings by Kadow and Abrams (1987) and would be consistent with a reduced contraction velocity of the detrusor muscle in BOO (Griffiths, 1977). Applying a multiple-comparison procedure, $\bar{a}$ proved to be lower ($P<0.001$) in both groups with BOO, B and A, than in the controls, but it also seemed to be higher ($P<0.01$) in Group A (unstable) than in Group B (stable) (Table 1, e). Such results suggest that the speed of detrusor contraction is relatively higher in the ODI patients. The parameter $\bar{a}$ was not reliable in distinguishing DI, however. The distribution of individual values of $\bar{a}$ in the various groups (Fig.) shows that no clear-cut limits exist which can differentiate between stable and unstable bladders. In the ODI patients, for example, individual values of $\bar{a}$ exceeding 2 standard deviations of the mean in Group B (0.94 ± 0.75 ml/s^2) were found in 8 subjects only (17%).

It has been suggested by Speakman *et al.* (1986) that ODI is a post-junctional supersensitivity phenomenon resulting from a condition of partial denervation, the latter probably being amenable to a state of raised intravesical pressure (Hârrison *et el.*, 1987). In the animal model, denervation supersensitivity is known to induce a decrease in electrical resistance between smooth muscle cells (Westfall, 1981). This might lead to enhanced synchronisation of detrusor contractions, which would explain why $\bar{a}$ tended to be higher in ODI than in stable obstructed bladders (Table 1, e).

In BPH, it would appear that the greater the

Table 2 Medians, Ranges and Significance Levels of Difference (Wilcoxon's rank sum test) for Parameter $\bar{a}$ in Obstructed Patients (Group A + Group B) and Controls (Group C)

Obstructed (n=86) *Median (range)*	*Controls (n=30)* *Median (range)*
1.08 (0.05–17.5)	2.64 (1.05–5.66)

$P<0.001$

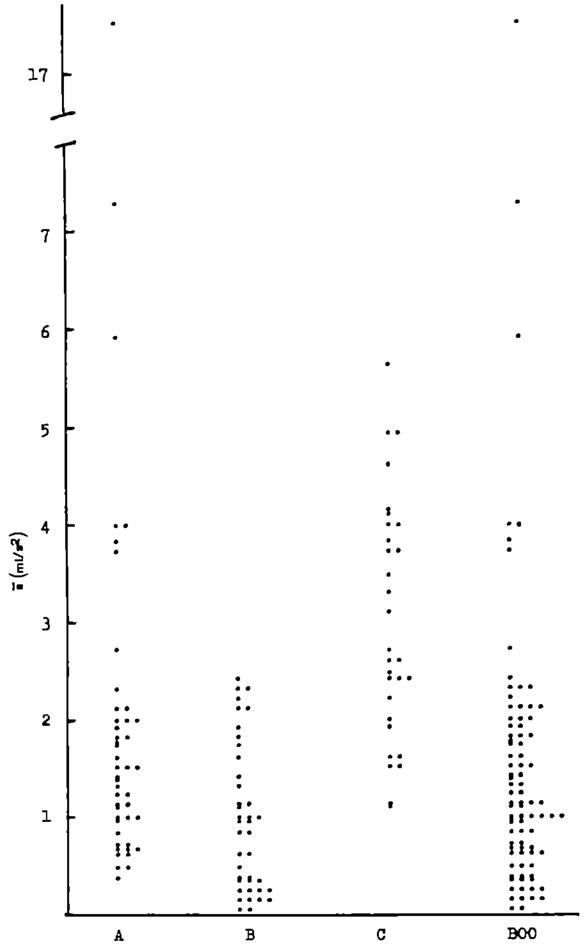


Fig. Distribution of individual values of $\bar{a}$ in Groups A (unstable, n = 46), B (stable, n = 40) and C (controls, n = 30) and in the obstructed patients as a whole (BOO, *i.e* Groups A and B).

obstruction the higher the chance not only for detrusor instability to develop (and thereby for altered electrophysiological properties, leading to a decreased electrical resistance between smooth muscle cells) but even for collagen fibres, infiltrating into the intracellular spaces, to upset easier electrical coupling. This would result in the acceleration of flow rate tending to be higher, on average, in the unstable obstructed bladders than in those that are stable, but would not give sufficient differences in the acceleration of flow rate to discriminate in individual patients between stable and unstable bladders.

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The Author

A. Cucchi, MD, Urologist, Policlinico S Matteo, I-27100 Pavia, Italy.

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Cystoplasty: Tubularisation or Detubularisation?

C. CHENG and H. N. WHITFIELD

Department of Urology, St Bartholomew's Hospital, London

Summary—Previous studies on substitution or augmentation cystoplasty have highlighted the profusion of surgical techniques available, but there is disagreement as to which is the best. We established an animal model to compare various types of cystoplasties, tubularised and detubularised, using ileum and caecum. Detubularisation did not abolish intrinsic bowel contractions but delayed their onset. No differences were noted in the frequency and amplitude of such contractions after detubularisation or between large and small bowel cystoplasties. Although intravenous urography did not demonstrate any abnormality in upper tract anatomy, a significant number of animals had some functional disturbance of the kidney after cystoplasty demonstrable on isotope renography, irrespective of the surgical technique. It may be possible to prevent these contractions with their associated harmful effects by preventing the bladder volume from building up excessively.

Substitution or augmentation cystoplasty using an isolated segment of bowel has been increasing in popularity (Goldwasser and Webster, 1986). A better understanding of bladder and bowel physiology, the introduction of clean intermittent self-catheterisation, the availability of artificial urinary sphincters and awareness of the long-term complications of urinary diversion have all contributed to an increasing enthusiasm for primary bladder reconstruction or undiversion. Numerous surgical techniques have been described, using almost all parts of the bowel, in differing lengths and configurations and in tubularised and detubularised forms (Goodwin *et al.*, 1959; Lilien and Camey, 1984; Light and Engelmann, 1986; Taguchi, 1987; Adams *et al.*, 1988). While there is disagreement as to which method is best, it is agreed that the ideal cystoplasty should provide an adequate capacity, day-time and night-time continence, a low end-filling pressure, preservation of renal function, efficient voiding and few side effects.

Many questions remain unanswered, particularly the long-term effects of cystoplasty using bowel. One popular idea is that the high pressure contractions which are present in the closed loop of a bowel segment are abolished or diminished by detubularisation. We examined the effects of detubularisation by establishing a number of surgical techniques in an animal model.

Materials and Methods

Minipigs were used because of the similarity between their kidneys and those of humans, in that they are multicaliceal and have an extrarenal pelvis (Terris, 1986). Receptors in the ureter, bladder and urethra are also similar (Larsen, 1979; Klarskov *et al.*, 1984).

Five surgical techniques were performed:

(1) Tubularised ileocystoplasty.
(2) Detubularised ileocystoplasty "U".
(3) Detubularised ileocystoplasty "W".
(4) Tubularised caecocystoplasty.
(5) Detubularised caecocystoplasty.

Fifteen animals were used, 3 in each operative group; 13 were female and all were operated on at weights of 10 to 20 kg. The animal was sedated with intramuscular ketamine or azaperone, anaesthesia was induced with intravenous metomidate hydrochloride (Hypnodil) and after intubation, anaesthesia was maintained with a mixture of

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halothane 2 to 3% with 2 l/min of oxygen and 2 l/min of nitrous oxide. Three doses of cefuroxime and metronidazole were given peri-operatively. Bowel preparation with castor oil was given the day before surgery.

In all animals a supratrigonal cystectomy was performed, thus eliminating the need for reimplantation of the ureters. For the ileocystoplasty a 30-cm segment of terminal ileum was isolated and was either anastomosed with the bladder remnant (Fig. 1) or incised along the antimesenteric border and fashioned into a "U" or "W" shaped flap (Fig. 2) before anastomosis with the bladder remnant. For the caecocystoplasty, caecum measuring 15 cm was used and in the detubularised form a corresponding length of terminal ileum was also isolated. Detubularisation was continued along the caecal wall and the ileal patch sewn on to the caecum (Figs 3 and 4).

Urea, electrolytes and urine culture were performed pre-operatively and 1, 4 and 7 months post-operatively. Intravenous urography, isotope renography using MAG3 and urodynamics were performed 1, 4 and 7 months post-operatively. At the end of 7 months, the animals were sacrificed for histology.

All investigations were performed under general anaesthesia. Intravenous urography involved the injection of 50 ml Conway 325 and plain, immediate and 15-min films were taken. Isotope renography required the animal to lie prone under the gamma camera with the head and body well supported on both sides to prevent movement; 150 MBq of MAG3 were injected intravenously and dynamic images taken at 10-s frames for 180 frames using a gamma camera (GE 400 AT). Following deconvolutional analysis, the parenchymal transit time index (PTTI), the whole kidney transit time index (WKTTI) and relative renal function were calculated (Whitfield *et al.*, 1978; Boddy *et al.*, 1988).

Preparation for urodynamics required general anaesthesia, after which the animal was woken up in a restraining cage before the test began. Anaesthesia was kept to a minimum to ensure rapid recovery. Following sedation, anaesthetic gases were delivered via a mask and intubation was dispensed with. Ultrasound-guided percutaneous insertion of bladder and intraperitoneal pressure lines was carried out using 16F epidural catheters inserted through a wide-bore needle. A "Longdwell" needle was used as a bladder filling line and the bladder was emptied as much as possible with a syringe. The lines were secured on the anterior

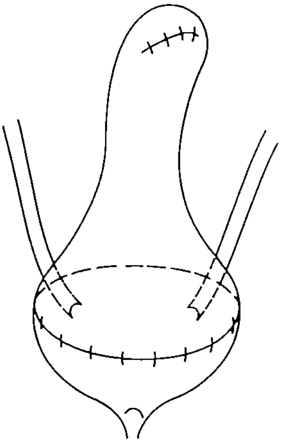

Fig. 1 Tubularised ileocystoplasty.

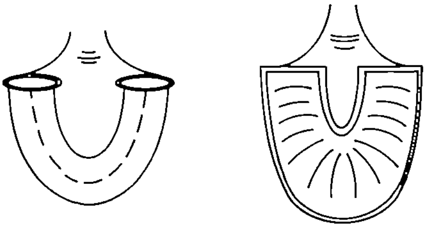

Fig. 2 Fashioning a "U" flap.

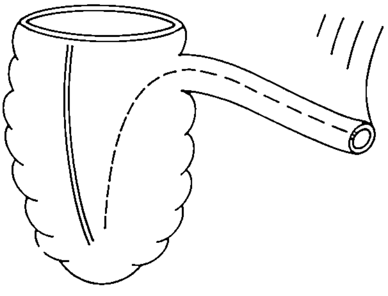

Fig. 3 Line of detubularisation along caecum and terminal ileum.

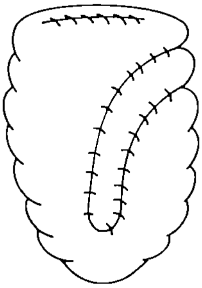

Fig. 4 Detubularised caecum.

abdominal wall with adhesive tape and the animal allowed to recover in the restraining cage. When awake, it was encouraged to stand and to eat while urodynamics were carried out. Urine voided on to the floor of the cage was collected in a measuring jug.

The urodynamic tracings were classified into 3 categories:

(I) Hyperactive—frequent, regular contractions usually accompanied by a rise in baseline pressure and leading to voiding (Fig. 5A).
(II) Active—infrequent contractions (Fig. 5B).
(III) Stable—flat tracing.

Results

Urea and electrolytes were normal in all animals. Urine culture, which was sterile in all animals preoperatively, showed a significant growth in 33 of 45 post-operative specimens, with a predominant growth of coliforms. Although intravenous urography showed normal upper tract anatomy in all animals, isotope renography showed that 43% had obstructive nephropathy (PTTI over 156 s) and 85% had pelvic retention (WKTTI over 170 s).

Urodynamics (Table)

Capacity. The capacity of the neobladder depended on the age and size of the animal and the length of the bowel segment used. It also depended on the length of time that had elapsed since surgery, since stretching of the neobladder wall occurred. In general, tubularised and detubularised cystoplasties resulted in a larger capacity (400–1300 ml) than occurs in the normal bladder (250 ml).

Table Comparison of Urodynamic Results

	Tubularised cystoplasty	*Detubularised cystoplasty*
Hyperactive	47% (9)	26% (6)
Active	16% (3)	26% (6)
Stable	37% (7)	48% (11)
Total	100% (19)	100% (23)

Figures in brackets refer to the total number of urodynamic studies that could be interpreted for tubularised and detubularised cystoplasties.

Volume at which contractions started. Contractions tended to occur later in detubularised cystoplasty (mean volume 575 ml) than in tubularised cystoplasty (mean volume 282 ml). This difference was noted only in ileocystoplasty.

Maximum amplitude of contractions. There was no significant difference between tubularised and detubularised versions.

Histology

Three animals died at 4 months, 1 with a perforated bladder (sustained during urodynamics) and aspiration pneumonia, while the other 2 went into respiratory arrest during isotope renography and no cause of death was discovered at autopsy.

All kidneys were macroscopically and microscopically normal.

All neobladders showed a mild inflammatory infiltrate in the lamina propria but no dysplasia or malignant changes.

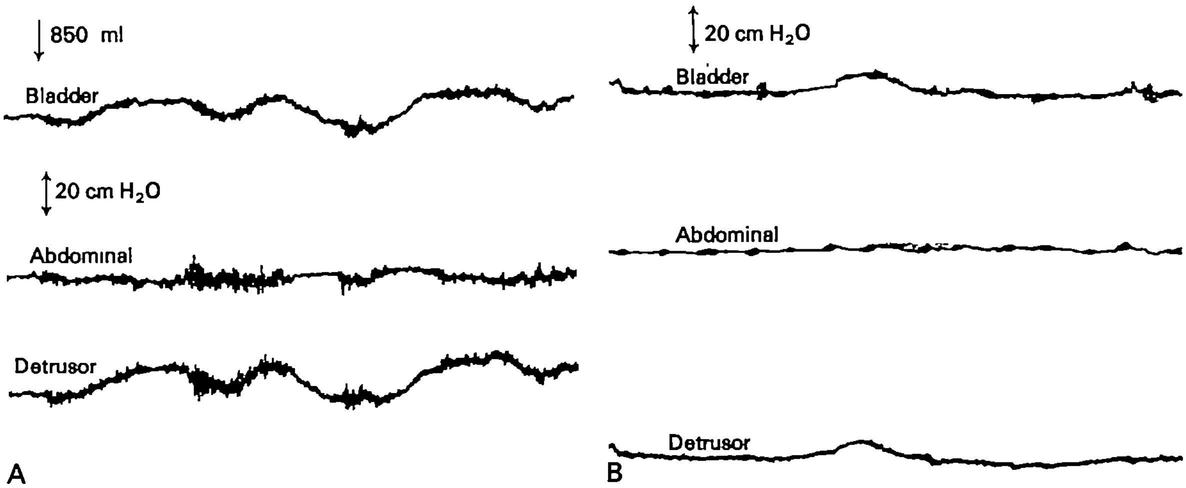

Fig. 5 (A) Hyperactive urodynamic tracing. (B) Active urodynamic tracing.

Discussion

That detubularisation of the small or large bowel segment does not completely abolish intrinsic bowel contractions has been noted in a number of studies (Light and Engelmann, 1985; Light and Scardino, 1986). While some cystoplasty patients did not appear to exhibit contractions in urodynamic investigations, day-time frequency, nocturia and nocturnal incontinence could well be manifestations of an unstable neobladder (Goldwasser *et al.*, 1986).

The findings in our animal work and also in patients are not surprising and can be explained by considering both the intrinsic contractility of the intestine and also the difference in capacity as a result of detubularisation.

Intrinsic contractility of the intestine

Small intestinal motility is a combination of phasic and tonal contractions, while the large intestine has both phasic and tonic segmental contractions on top of mass contractions (Hinman and Oppenheimer, 1958; Kock *et al.*, 1968). However, large and small bowel are similar in that contraction is involuntary and results from distension. The more the distension, the stronger the contraction. As the contents are being emptied during a contraction wave, distension is reduced and so is the contractility. This differs from the detrusor in that the latter does not contract during filling and contraction, when it occurs, is voluntary (*i.e.* during voiding) and the contractility is sustained until the bladder empties to completion (Turner-Warwick, 1979).

The electrical activity in the wall of both small and large bowel starts in the longitudinal muscle and spreads to the circular muscle, and the effect is to produce a co-ordinated contraction and concentric narrowing of the lumen. If the bowel wall is detubularised by being incised along the antimesenteric border, the circular smooth muscle is disrupted and electrical activity originating in the longitudinal muscles then spreads along only half of the circumference of the wall. Contractions thus become unco-ordinated and disorganised (Hinman, 1988). Nevertheless, contractions are not entirely abolished and when sufficient distension occurs during filling, contraction waves can be seen. In this study, contractions occurred at a later stage (*i.e.* larger volume) in detubularised cystoplasty. One reason for this is that detubularisation results in a larger capacity and hence a greater bladder volume needs to be reached before the same degree of wall distension occurs, the latter bringing about the contractions.

Difference in capacity resulting from detubularisation

A recent report on the geometry of cystoplasty showed that by detubularisation and arranging the intestinal flap to form a sphere, the volume increased because a sphere has the highest volume:surface area ratio (Koff, 1988). While the volumetric gain described as a result of detubularisation may be optimistic in reality, the fact remains that the capacity of the neobladder is enhanced when a detubularised segment rather than a tubularised segment is used. This allows the detubularised neobladder to fill up to a greater capacity before the wall is distended to the same extent as in the tubularised version, and this contributes to the delay in the onset of contraction waves. By preventing an excessive build-up of bladder volume it may be possible to prevent the onset of these pressure waves with their possible deleterious effect. This can be achieved by frequent voiding or by intermittent self-catheterisation.

Taking into consideration the altered contractility, increased capacity, compliance and accommodation, detubularised cystoplasty is preferable to tubularised cystoplasty in that the former has less contractility, a later onset of contractions and a larger capacity.

The significance of contraction waves is manifold. If the pressure rise exceeds that of the urethral closure pressure, incontinence occurs. This is commonly seen in tubularised cystoplasties (Light and Engelmann, 1985) and may be worse at night. It may give rise to the feeling of urgency if bladder sensation is intact, resulting in day-time and night-time frequency. Most worrying is the effect these pressure rises may have on the upper tract, with or without reflux. A significant rise in intravesical pressure may impede ureteric drainage and result in obstructive nephropathy in the absence of vesicoureteric reflux (Jones *et al.*, 1988). The present study shows that over 80% of the animals had pelvic retention and over 40% had obstructive nephropathy. However, we could not find any correlation between renal dysfunction and the type of surgical technique used or between whether the cystoplasty was tubularised or detubularised. Other factors may have been involved; a distended bladder was present in all of the animals undergoing isotope renography; halothane results in relaxation of the detrusor and hence further bladder distension (Doyle and Briscoe, 1976) and the compression effect of the support placed under the animal's abdomen to prevent movement during renography. While the majority of the animals had some degree of renal dysfunction, it was interesting to see that intravenous urography, which shows upper tract anatomy, was normal, as were urea and electrolytes. Isotope renography is the most sensitive indicator of renal function.

The following conclusions were reached. Augmentation cystoplasty by all methods increases the neobladder capacity. Detubularisation does not abolish intrinsic bowel contractions. It delays the onset of bowel contractions and produces no change in the amplitude of contractions. All cystoplasties, tubularised or detubularised, are associated with a risk of upper tract obstruction.

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The Authors

C. Cheng, FRCS, Research Registrar
H. N Whitfield, MA, MChir, FRCS, Consultant Urologist.

Requests for reprints to: C. Cheng, Department of Urology, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE.

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Clinical Study of Prognostic Factors of Superficial Bladder Cancer Treated with Intravesical Bacillus Calmette-Guerin

T. SHINKA, A. HIRANO, Y. UEKADO and T. OHKAWA

Department of Urology, Wakayama Medical College, Wakayama, Japan

Summary—Intravesical instillation of Tokyo 172 strain Bacillus Calmette-Guérin (BCG) was performed in 96 patients with initial superficial bladder cancer (Ta and T1) after transurethral resection (TUR) of tumour as a prophylaxis against tumour recurrence. The recurrence rate of tumours was estimated by the person-years method, comparing it with that of historical controls. There were statistically significant decreases in recurrent tumours following BCG therapy.

To clarify the efficacy of intravesical BCG therapy, the prognostic significance of several factors was evaluated in patients with bladder cancer treated with TUR and instillation of BCG. The prophylactic effects were statistically better for those with multiple tumours, grade 3 lesions or Ta lesions than for control patients. No correlation between purified protein derivative (PPD) responsiveness and favourable results could be observed.

Our results suggest that intravesical BCG instillation can alter the biological behaviour that affects the recurrence of superficial bladder cancer, especially for multiple, high grade or Ta tumours.

The reported recurrence rate of superficial bladder cancer after transurethral resection ranges from 30% when the original tumour is solitary and of low grade to more than 90% when there are multiple high grade tumours (Soloway, 1988). In addition, most tumours recur within 2 years after TUR (Utz and De Weerd, 1978). In recent years, intravesical Bacillus Calmette-Guérin therapy for superficial bladder cancer, introduced by Morales *et al.* (1976), has attracted attention as one of the most effective adjuvant treatments for preventing its recurrence (Haaff *et al.*, 1985).

We reported the effectiveness of intravesical BCG therapy, using Tokyo 172 strain BCG, in preventing the recurrence of superficial bladder cancer after TUR (Shinka *et al.*, 1989). In the present study, the results of intravesical BCG therapy, performed in 96 patients with initial superficial bladder cancer (stage Ta, T1) to prevent recurrence after TUR, were compared with those in the control groups, evaluating various factors involved in the efficacy of this therapy and discussing indications and selection of patient.

Patients and Methods

The study group consisted of 96 patients with primary superficial transitional cell carcinoma of the bladder who underwent TUR followed by intravesical BCG instillation as adjuvant therapy. The control group comprised 102 patients with superficial transitional cell carcinoma of the bladder who underwent TUR as initial treatment, of whom 74 were treated by intravesical chemotherapy (29 with doxorubicin hydrochloride, 17 with mitomycin C and 28 with mitomycin C + ancitabine hydrochloride) after TUR (other drug instillation group) and the remaining 28 by TUR alone (non-instillation group). The characteristics of the 96 patients treated by intravesical BCG therapy and the 102 in the control groups are shown in Table 1.

The bladder was emptied by catheterisation and

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80 mg of Tokyo 172 strain BCG ($5–12 \times 10^7$ colony forming units/mg, Nihon BCG Co., Japan) suspended in 40 ml saline were injected into the bladder 7 days after TUR. The patients were instructed to retain the drug for 2 h. In principle, BCG therapy was performed once weekly for 6 weeks. The patients were then followed up by urinary cytology and cystoscopy every 3 months. The purified protein derivative skin test was performed before and after the 6-week course of intravesical BCG.

The simple recurrence rate and the recurrence rate by the person-years method (Schoenberg and Myers, 1977) during the 2-year period after BCG therapy were calculated. The results were compared with those in the control groups. Significant differences in the simple recurrence rate were evaluated by χ^2 test. In the person-years method, the ratio of the observed actual value to expected value (O/E) was calculated using the following equation and significant differences were evaluated using the Poisson distribution table:

$$O/E = (\text{the number of recurrences after BCG therapy}) / \{(\text{the recurrence rate in the control}) \times (\text{total patient-months after BCG therapy})\}.$$

Results

No significant difference was observed in each variate distribution by χ^2 test between the 96 patients receiving BCG treatment and the 102 controls, showing no bias of patients (Table 1).

The recurrence rate during the 2-year period after TUR and BCG treatment in 96 patients was compared with that in each control group (Table 2). The simple recurrence rate was significantly lower in the BCG group (21/96 patients, 22%) than in either the drug instillation group (34%) or the non-instillation group (46%). The number of recurrences/total patient-months was also significantly lower in the BCG group (0.019) than in the drug instillation group (0.030) or in the non-instillation group (0.043), with OE ratios of 0.619 and 0.446 respectively.

To evaluate various factors associated with the efficacy of BCG therapy, the recurrence rate according to tumour multiplicity, grade or stage was compared between the BCG group and each control group (Table 3). The recurrence rate of multiple tumours was higher than that of solitary tumours in each group. In the BCG group, the recurrence rate of solitary tumours was similar to that in one control group, but the rate of multiple tumours was significantly lower than in both control

Table 1 Distribution of Pre-treatment Characteristics of 96 BCG Patients and 102 Controls

		Controls	
	BCG instillation group (%)	*Other drug instillation group (%)*	*Non-instillation group (%)*
No. of patients	96	74	28
Sex			
Male	82 (85.4)	65 (87.8)	25 (89 3)
Female	14 (14.6)	9 (12.2)	3 (10.7)
Mean age (years)	66 3	64.1	64.7
	26–91	19–84	41–92
Multiplicity			
Solitary	42 (43.7)	36 (48.6)	13 (46.4)
Multiple	54 (56 3)	38 (51.4)	15 (53.6)
Tumour grade			
G1	45 (46.9)	33 (44.6)	18 (64.3)
G2	35 (36.4)	28 (37.8)	6 (21.4)
G3	16 (16 7)	13 (17.6)	4 (14.3)
Tumour stage			
Ta	47 (49.0)	34 (45.9)	16 (57.1)
T1	49 (51.0)	40 (54.1)	12 (42.9)
associated with Tis	10	4	2
Follow-up (months)	13.9	18.8	19.2
	1.7–24	0.4–24	0.5–24

Table 2 Recurrence Rate in 96 Patients in the 2 Years following BCG Therapy and Comparison with 102 Controls

	No of patients	*No. with recurrent tumours*	*Recurrence rate (%)*
Simple recurrence rate			
BCG patients	96	21	21.9
Controls			
Other drug instillation group	74	26	35.1
Non-instillation group	28	13	46.4
BCG group versus other drug group		$P<0.05$	
BCG group versus non-instillation group		$P<0.01$	

	Total no of recurrences	*Total no of patient – months*	*No of recurrences/ patient – months*
Person – years method			
BCG patients	25	1,331.2	0.019
Controls			
Other drug instillation group	42	1,393.0	0.030
Non-instillation group	23	538.5	0.043
BCG group versus other drug group		O/E = 0.619	$P<0.05$
BCG group versus non-instillation group		O/E = 0.446	$P<0.01$

O: Number of recurrences following BCG.
E: Expected value = (recurrence rate in control) X (patient-months of BCG patients).

groups. In the control groups, the recurrence rate tended to increase when the tumour grade was high. The recurrence rate of G3 tumours in the BCG group was significantly lower than that in each control group. With regard to tumour stage, the recurrence rate of Ta tumours in the BCG group was significantly lower than that in the non-instillation group but did not differ significantly

Table 3 Comparison of Recurrence Rate According to Tumour Multiplicity, Grade or Stage between BCG Patients and Control Groups

	BCG instillation group		*Other drug instillation group*		*Non-instillation group*	
	No. of patients	*No. of tumour recurrences (%)*	*No. of patients*	*No of tumour recurrences (%)*	*No. of patients*	*No. of tumour recurrences (%)*
Multiplicity						
Solitary	42	7 (16.7)	36	7 (19.4)	13	5 (35.5)
Multiple	54	14 (25.9)	38	19 (50.0)	15	8 (53.3)
BCG group versus other drug group				Solitary NS; Multiple $P<0.05$		
BCG group versus non-instillation group				Solitary NS; Multiple $P<0.05$		
Tumour grade						
1	45	9 (20.0)	33	10 (30.3)	18	6 (33.3)
2	35	10 (28.6)	28	9 (32.1)	6	4 (66.7)
3	16	3 (18.8)	13	7 (53.8)	4	3 (75.0)
BCG group versus other drug group				G1 NS, G2 NS; G3 $P<0.05$		
BCG group versus non-instillation group				G1 NS; G2 NS; G3 $P<0.05$		
Tumour stage						
Ta	47	8 (17.0)	34	9 (26.5)	16	8 (50.0)
T1	49	14 (28.6)	40	17 (42.5)	12	5 (41.7)
associated with						
Tis	10	2 (20.0)	4	2 (50.0)	2	2 (100)
BCG group versus other drug				Ta NS, T1 NS; Tis NS		
BCG group verus non-instillation group				Ta $P<0.01$; T1 NS, Tis $P<0.05$		

NS: not significant

from that in the other drug instillation group. The recurrence rate of T1 tumours did not significantly differ among the groups.

Carcinoma *in situ* was found in 10 patients in the BCG group and 6 in the control groups; 2 patients in the BCG group and 4 in the control groups developed recurrences.

The PPD skin test was performed before BCG therapy in 82 patients, of whom 57 (70%) were positive and 25 (31%) were negative (Table 4). The tumour recurrence rate after BCG treatment did not differ between the positive patients (19%) and negative patients (20%). Positive conversion was observed after BCG therapy in 11 of the 25 patients, of whom 3 (27%) showed recurrence. The tumour did not recur in any of the other 5 patients who remained negative after this therapy.

Discussion

Recurrence of superficial bladder cancer is well known. Multiple tumours usually recur more often than solitary tumours, high grade tumours more frequently than low grade tumours, and stage T1 tumours more frequently than stage Ta (Lutzeyer *et al.*, 1982; Heney *et al.*, 1983; Soloway, 1988). In the present study, similar tendencies were observed in the 28 controls treated by TUR alone.

Torrence *et al.* (1988) evaluated prognostic factors involved in tumour recurrence and progression after intravesical BCG therapy and observed no association of tumour stage or grade with the effectiveness of treatment. However, they did not compare the results with those of controls. Soloway and Perry (1987) reported that the likelihood of a complete response to BCG was better for those with initial Ta lesions and carcinoma *in situ* than for patients with initial T1 lesions. We compared the recurrence rate between the BCG group and non-instillation group and observed a significantly lower recurrence rate in the former with respect to multiple tumours, G3 tumours or Ta tumours. In addition, comparison with the other intravesical chemotherapy group showed a significantly lower recurrence rate for multiple and G3 tumours. These results suggest that intravesical BCG therapy can alter the biological behaviour of superficial bladder cancer.

Table 4 Purified Protein Derivative (PPD) Skin Test Responsiveness and Tumour Recurrence Rate before and after BCG Therapy

	No. of patients	*No. of recurrences (%)*
Previously PPD sensitised	57	11 (19.3)
Previously PPD non-sensitised	25	5 (20.0)
PPD conversion	11	3 (27.3)
PPD non-conversion	5	0 (0)
Unknown	9	2 (22.2)
PPD skin test not done	14	5 (35.7)
Total	96	21

The efficacy of intravesical BCG for carcinoma *in situ* of the bladder is making it an appropriate alternative to radical surgery as first-line treatment (Herr *et al.*, 1986). In our results, although carcinoma *in situ* was confirmed in only 10 patients in the BCG group, the recurrence rate in this group was lower than that in the non-instillation group treated by TUR alone. The effectiveness of BCG in treating multiple, G3 and Ta tumours in this series is consistent with the results in treating carcinoma *in situ* of the bladder.

On the other hand, limitations of BCG therapy have been also reported. Catalona *et al.* (1987) reported good results in patients who had failed only 1 course of BCG therapy but a high risk of invasion and metastasis in those who had failed 2 or more courses, suggesting that patients in the latter group should be considered for alternative therapy. Herr *et al.* (1989) performed multivariate analysis and demonstrated that T1 tumours responded poorly to BCG therapy. We also found no significant difference in the recurrence rate of T1 tumours between the BCG group and controls and could not demonstrate the efficacy of BCG in treating T1 tumours. This may suggest unresponsiveness of T1 tumours to BCG, although neither muscle invasion nor metastasis was observed in our series. In this study, the observation time was the 2-year period after BCG therapy during which the recurrence rate is high. To evaluate the limitations of this therapy, the observation period should exceed 2 years.

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The Authors

T. Shinka, MD, Associate Professor.
A. Hirano, MD, Assistant Professor
Y. Uekado, MD, Assistant Professor.
T. Ohkawa, MD, Professor and Chairman, Department of Urology.

Requests for reprint to: T. Shinka, Department of Urology, Wakayama Medical College, 27-Nanabancho, Wakayama City, 640 Japan

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Fractionated Urinary Cytology in the Follow-up of Bladder Cancer

K. J. HASTIE, R. AHMAD and C. U. MOISEY

Department of Urology, Royal United Hospital, Bath

Summary—Cytological examination of voided urine is an established investigation in urological practice. In a pilot study of 50 patients with histologically proven transitional cell carcinoma of the bladder, urine cytology was undertaken on samples from the initial, mid-stream and terminal parts of the void. Analysis showed that although the cell density varied between the samples in some cases, no part of the void was consistently richer in benign or malignant cells and similar cell types were seen in every sample from any given patient. It was concluded that fractionated cytology did not improve the diagnostic accuracy of urinary cytology and that any sample of urine was suitable for cytological purposes.

Cytological examination of voided urine is an established investigation in the diagnosis and follow-up of bladder tumours. Although urine sampling for cytology is simple and non-invasive, false positive and false negative rates approaching 15 and 48% respectively have been reported even when the specimens were examined by experienced cytologists (Loening *et al.*, 1978).

Clearly, any modification of the technique which results in greater diagnostic yield would be of value. A pilot study was undertaken to compare the cytology from the initial, mid-stream and terminal sections of the void (fractionated cytology) to assess whether any one part of the urine stream gave more consistent and reliable results.

Patients and Methods

The study group included 50 patients admitted consecutively for check cystoscopy. All had biopsy proven transitional cell carcinoma of the bladder and the mean age was 71.9 years (range 44–90).

Pre-operatively, all patients were instructed to provide 3 urine samples from the same void into separate, clearly marked pots, thus sampling the initial, mid-stream and terminal parts of the stream. In all cases a mid-stream sample was collected and cultured to exclude infection.

The cytology samples were examined independently by 1 of 2 experienced cytologists. Those specimens considered highly suggestive of malignancy were, for the purposes of this study, included with those urines which were unequivocally positive for malignant cells. Subsequently the patients underwent check cystoscopy and the results were compared.

Results

Previous histology in the group of patients showed that 25 had grade I lesions, 17 grade II and 8 grade III. On this occasion, 29 patients had a recurrence diagnosed at cystoscopy. More than half of the patients with recurrence (16) had positive cytology and the correlation between positive cytology and recurrence at cytoscopy was closely related to previous histological grade (Table 1). There were 12 false negative cytologies (24%) and 1 false positive. In 3 patients, pus obscured the cellular details and these patients, only 1 of whom had recurrence at cystoscopy, were studied no further. With these exceptions, the overall sensitivity in patients with proven recurrence at cystoscopy was 57%, but all of those with previous grade III lesions and positive cytology had cystoscopic recurrence. The cytological results were analysed further with regard to fractionation. In all cases, identical cells were observed in all 3 samples from each patient.

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Table 1 Comparison between Cytology and Cystoscopy in Relation to Tumour Grade

	Prior tumour grade		
Investigation results	*I (n=22)*	*II (n=17)*	*III (n=8)*
True positive	2	6	8
False negative	10	2	0
True negative	10	8	0
False positive	0	1	0

True positive = cystoscopic recurrence with positive cytology.
False negative = cystoscopic recurrence with negative cytology.
True negative = cystoscopy clear with negative cytology.
False positive = cystoscopy clear with positive cytology.

In any given case, therefore, if only 1 specimen had been examined, the cytological report would have been the same. In 9 of those with positive cytology, variations in the cellularity were noted between the samples, with 2 patients having proportionally more cells in the initial sample, 4 in the mid-stream sample and 3 in the terminal sample (Table 2). Nevertheless, if malignant cells were detected in one specimen, they were visible in all and all samples examined in the 12 patients with false negative cytology failed to show any malignant cells.

Discussion

Cytological examination of urine continues to be of value as it is non-invasive, easily repeated and theoretically examines the entire urothelium. The sensitivity of urinary cytology varies widely between reported series (26–100%), with a false positive rate of up to 12% (Kern *et al.*, 1968; Harris *et al.*, 1971; Lewis *et al.*, 1976). The accuracy of urine cytology is strongly dependent upon histological grade and the positive rate approaches 100% in carcinoma *in situ* (Koss *et al.*, 1985).

A study by the National Bladder Cancer Collaborative Group A (1977) reported that the sensitivity of cytology was 43% for grade I and grade II lesions; this is in stark contrast to a sensitivity of 93% in grade III disease. False positives may be related to the experience of the cytologist and the criteria used in cytodiagnosis. Similarly, the results may be less reliable in the presence of infection. Positive cytology is known to precede macroscopic disease in some cases (Murphy *et al.*, 1984).

A number of techniques have been used to enhance the reliability of urine cytology, including bladder washing with saline or other irrigants, the examination of repeated specimens and even vigorous exercise prior to sampling (Lewis *et al.*, 1976). Typically, however, samples for urine cytology are mid-stream specimens, often taken at the same time as a urine culture. The possibility that there may be greater or lesser numbers of cells expelled at different points during the urine flow has not, to our knowledge, been previously explored.

Table 2 Fractionated Cytology

Sample with maximal cellularity	*No. of patients*
Initial	2
Mid-stream	4
Terminal	3
Cellularity equal	8

All cases cytology positive.

This study has again demonstrated that urine cytology alone is inadequate for follow-up of many patients with previous bladder tumours, as shown by the high false negative rate.

It has also been shown that the yield is not improved by fractionated sampling and that any part of the voided stream is adequate for cytological purposes.

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The Authors

K J Hastie, MD, FRCS, Registrar.
R. Ahmad, FRCS, Honorary Senior House Officer.
C. U. Moisey, FRCS, Consultant Urologist

Requests for reprints to: K. J. Hastie, Department of Urology, Royal Hallamshire Hospital, Sheffield S10 2JF.

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Computed Tomography and Magnetic Resonance Imaging before Salvage Cystectomy

A. K. DIXON, A. M. DEANE and P. T. DOYLE

Departments of Radiology and Urology, Addenbrooke's Hospital and the University of Cambridge, Cambridge

Summary—Nine patients who developed recurrence of bladder carcinoma following radical radiotherapy were assessed for salvage cystectomy by computed tomography (CT) and magnetic resonance imaging (MRI) to predict extravesical spread. Both tests correctly identified a patient with such advanced local disease that surgery was deemed inappropriate at examination under anaesthesia and both tests indicated that surgery might be difficult in a further patient with inoperable disease. Both tests demonstrated abnormalities in the perivesical and pelvic fat planes in all patients but they had difficulty in distinguishing between malignant infiltration and the effects of radiotherapy. Nevertheless, each test is useful in excluding gross pelvic disease and predicting involvement of adjacent organs. The advantages of the multiplanar images provided by MRI must be balanced against the high cost. CT readily demonstrates the upper abdomen, the kidneys and para-aortic nodes as well as the pelvis and is more widely available.

Computed tomography and magnetic resonance imaging are now extensively employed in the preoperative assessment of bladder carcinoma (Bryan *et al.*, 1987; Hendrix *et al.*, 1989). There is less information about their use in the assessment of tumours which recur after radiotherapy. The interpretation of CT can be difficult following radiotherapy as the normal tissue planes may become obscured by fibrosis (Dixon and Nightingale, 1984). Although the fibrosis caused by radiotherapy is usually symmetrical in the axial plane, the identification of tumour in this setting is difficult until the tumour bulk is so great that asymmetric abnormalities are present. It is likely that MRI will have similar limitations, although some workers claim that viable tumour might be recognised by yielding a higher signal intensity than fibrotic material, especially on T_2 weighted images (Ebner *at al.*, 1988). Hence the interest in studying a series of patients who were being assessed for possible salvage cystectomy by CT and MRI to evaluate the relative contributions of these techniques.

Patients and Methods

Nine patients, ranging in age from 46 to 74 years (mean 60.33) who developed recurrent bladder tumour (all transitional: 1 well, 1 moderately, 7 poorly differentiated) at a mean interval of 10.4 months (range 3–26) following conventional radical radiotherapy were studied with CT and MRI as pre-operative assessment.

CT was performed according to a standard protocol (Dixon, 1983) on a Siemens Somatom II. This employs slices 0.8 cm thick at 2 cm intervals through the para-aortic region and 1.5 cm intervals in the pelvis. Intravenous contrast medium was used as appropriate. The report of this initial study was used for a clinical decision but at the end of the study, before the surgical findings were revealed, the CT images were analysed (A.K.D.) with special references to nodal status, ureteric dilatation, involvement of adjacent organs and the integrity of fat planes around the bladder. Abnormal fat planes were subjectively graded (mild, moderate or severe changes); the presence or lack of symmetry was noted. An overall opinion as to operability was also made. This analysis was made at the time of follow-up, several weeks after the MRI study, but before knowledge of the operative findings.

Based on a Poster Demonstration at the 45th Annual Meeting of the British Association of Urological Surgeons in St Helier, June 1989

MRI was performed on a Picker 2055 HP rampable machine (Dixon *et al.*, 1988) operating at 1.5T. A series of contiguous axial images 10 mm thick through the bladder was obtained using the well established dual-echo technique in all patients; this provided spin density (TR—repetition time—2000 ms/TE—echo time—20 ms) and T_2 weighted images (TR 2000 ms/TE 80 ms). This was followed by a series of contiguous sagittal images, either using a similar dual-echo sequence (3 patients) or using a T_1 weighted spin-echo sequence (TR 700 ms/TE 26 ms, 6 patients). Further imaging planes and sequences were also employed in some patients. The MRI report (A.K.D.) addressed the same points as the detailed CT (see above). MRI followed CT within a week in 6 of the 9 patients and at 3, 5 and 6 weeks for the other 3 patients.

After CT and MRI all patients had an examination under anaesthesia (EUA) before surgery. In the 8 patients with an apparently operable tumour, an attempt was made to remove the bladder and locate any nodal and extravesical tumour. The mean interval between MRI and surgery was 2.2 weeks (range 0–6). In 1 of the 8 patients who proceeded to surgery the lesion proved to be locally inoperable but in the remaining 7 patients either an ileal loop conduit was formed or a "neo-bladder" was fashioned from small bowel by a pouch technique (enterocystoplasty).

The resulting 7 surgical specimens were examined histopathologically with particular emphasis on whether the margins of the block were free of tumour.

Results

Diagnostic quality CT and MRI images proved possible in every patient. Some of the results are shown in the Table. Illustrative examples are shown in Figures 1 and 2.

CT showed normal pelvic nodes in 7 of the 9 patients. In 2 patients there was minimal enlargement of internal iliac nodes; 1 of these patients was found to be inoperable at EUA; in another patient enlarged nodes were reported on the right while the surgeon encountered more marked left internal iliac nodal enlargement. MRI also demonstrated internal iliac nodal enlargement in these 2 patients. However, in an additional patient a small cluster of nodes in the right internal iliac region was reported as suspicious, although no one node measured over 1 cm across. At surgery, cystectomy was possible but the excision was incomplete, with tumour extending posteriorly into the extravesical fat. Both CT and MRI missed 1 patient with involved 5-mm nodes in the right pelvic side wall.

Involvement of adjacent organs was correctly predicted by both CT and MRI in 4 patients. The prediction was precise in 2 patients (prostate, Fig. 1; vagina/cervix, Fig. 2) but the correlation was less precise in 2 others. In 1 patient, both tests had suggested right seminal vesicle involvement but at laparotomy the lesion was inoperable and this region could not be closely inspected. In another patient both tests had questioned the appearances of the adjacent sigmoid colon and surrounding fat; at surgery there was quite extensive left-sided extravesical spread with incomplete excision at the resected margin. In 1 further patient there was slight discordance between the CT and MRI findings; CT had raised the possibility of anterior abdominal wall involvement; this is a difficult assessment on axial imaging; the sagittal images provided by MRI were reassuring here. In the other 4 patients both CT and MRI correctly predicted the adjacent organs to be free from direct involvement.

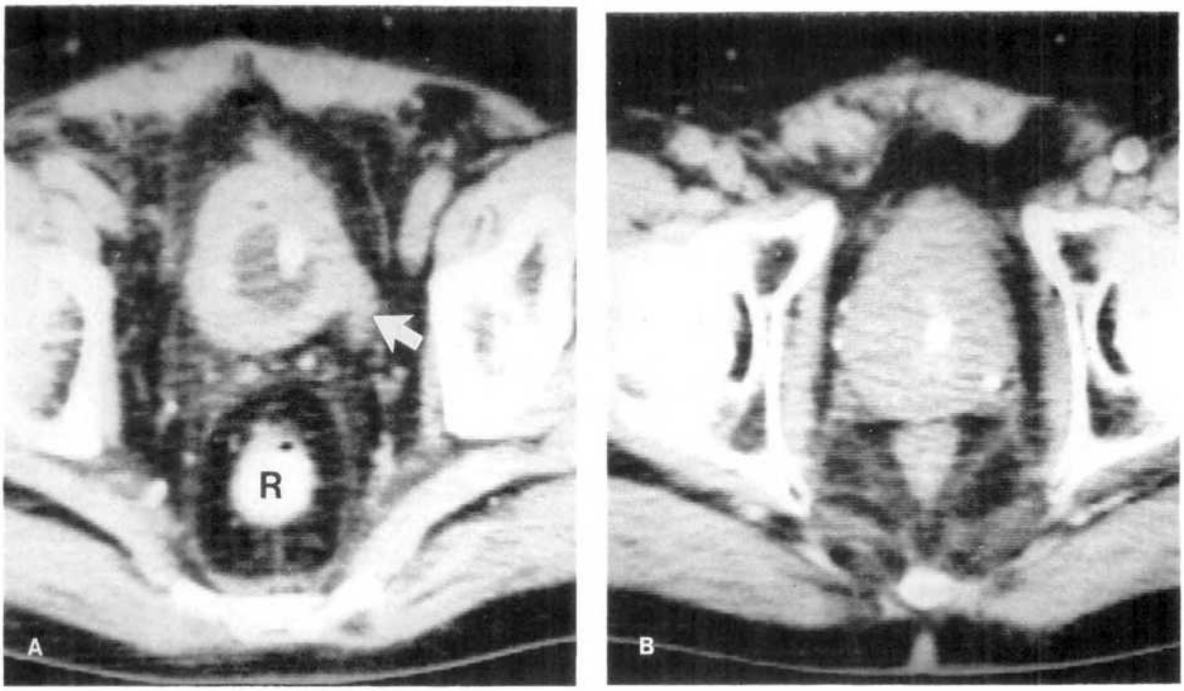
Both techniques correctly predicted the presence or absence of ureteric dilatation in all 9 patients; 3 of the 8 patients who underwent surgery had unilateral dilatation; the patient with inoperable tumour had bilateral dilatation.

The perivesical and other pelvic fat planes (*e.g.* the perirectal fibrous sling) appeared abnormal in

Table CT, MRI and Surgical Findings in the 8 Patients who Proceeded to Laparotomy

	Involved pelvic nodes	*Involved adjacent organs*	*Obstructed ureters (n=16)*	*Abnormal fat planes*	
				Symmetry	*Asymmetry*
CT	1	4	3	6	2
MRI	2	3	3	6	2
Surgery	3	3	3	2 Tumour 4 Radiotherapy	2 Tumour

The ninth patient, whose tumour was deemed inoperable at CT, MRI and EUA, is not included.



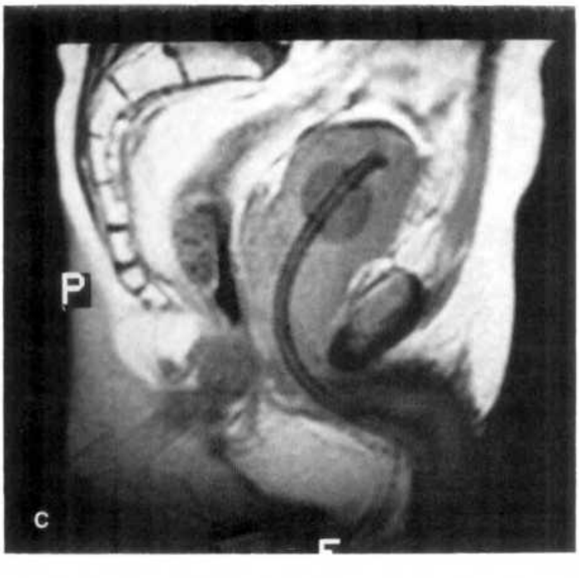


Fig. 1 A patient whose recurrent tumour involved the prostate. (A) Computed tomogram through the small thick-walled bladder (water-filled balloon catheter *in situ*) just cranial to the seminal vesicles. The dilated distal left ureter is visible (arrow). Note the prominence of the peri-rectal fibrous sling producing the "halo" effect; the contrast-filled rectum (R) is surrounded by normal peri-rectal fat; the para-rectal fat, peripheral to the thickened peri-rectal sling, is abnormal (graded moderate). In this patient these relatively symmetrical alterations in fat planes proved to be due to radiation change. (B) CT at a more caudal level. The small bladder merges with a very large prostate, suggesting the presence of tumour extension into the prostate. (C) Sagittal MR (spin density) showing the confluence of the small thick-walled bladder with the enlarged prostate. Again tumour extension was predicted. This patient is doing well following complete resection of the bladder and prostate.

all patients on both techniques. The correlation between CT and MRI was exact, apart from 2 patients in whom MRI showed severe changes while CT suggested moderate change. Attempts to differentiate between tumour infiltration and radiation effect were unrewarding unless the appearances were asymmetric due to tumour infiltration.

As regards operability, both CT and MRI correctly identified the one patient who was considered inoperable at EUA. They also both identified several abnormalities (nodal enlargement, seminal vesicle involvement and asymmetric alterations in fat planes) in the one patient deemed inoperable at laparotomy. Allusion has already been made to the patient in whom CT indicated possible anterior abdominal wall involvement.

Histopathogical examination revealed tumour up to the margins of the excised specimen in 3 of

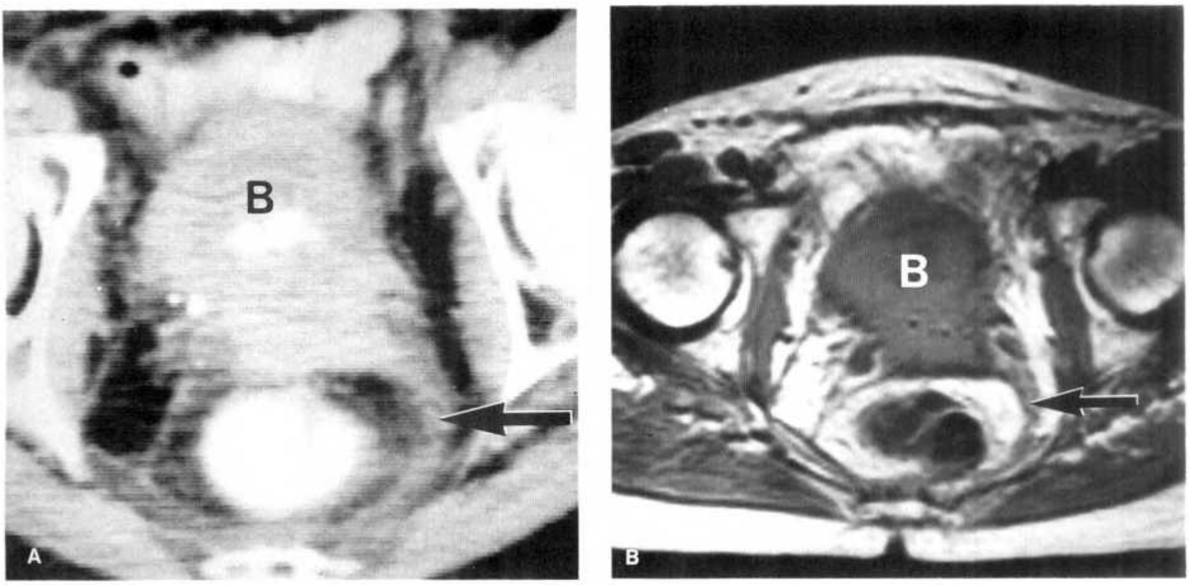


Fig. 2 The single patient deemed inoperable at examination under anaesthesia who did not proceed to surgery. Both CT (A) and MRI (B: spin density) show loss of the normal fat plane posterior to the bladder (B) in this female patient. There is an extravesical mass (in contiguity with the recurrent bladder tumour) which engulfs the upper vagina/cervix. Both ureters were obstructed. Note the asymmetric thickening of the region of the left uterosacral ligament (arrow). This patient had a fixed mass at examination under anaesthesia and was deemed inoperable. The patient has since died.

the 7 patients whose bladders could be resected. Only in 1 of these 3 patients was such extensive disease correctly predicted by pre-operative imaging; this was the patient in whom both CT and MRI had revealed abnormal fat adjacent between the bladder and sigmoid colon.

Discussion

Salvage cystectomy is not a commonly performed operation and the prognosis is gloomy. Even with careful pre-operative investigation, the outcome is poor; 5 of our 9 patients have already died (4 from tumour dissemination); 1 has known metastases; 3 are well and seemingly metastasis-free.

It would be ideal to have a test which could identify nodal involvement, but none, at present, is able to detect micrometastases within a node of normal size. CT and MRI can identify enlarged nodes but this could be caused by tumour involvement or inflammatory disease. The numbers in this study are small and the surgical findings are inevitably imprecise after radiotherapy. Nevertheless, enlarged nodes were identified in 2 patients. It is highly likely that nodal involvement was present (and missed by CT and MRI) in some of the other 7 patients, expecially in the 2 who have since died of metastases and 1 with known tumour dissemination. It is impossible from our data to say whether CT or MRI is better at identifying nodal enlargement; MRI does have the advantage of being able to confirm probable lymphadenopathy, seen on one sequence, by judicious choice of additional sequences or imaging planes; MRI is known to be better than CT at distinguishing between nodal material and vessels (Lee *et al.*, 1984).

The key criterion for salvage cystectomy is the presence or absence of involvement of adjacent organs and both tests fared quite well here. In 2 patients the sagittal plane provided by MRI (Fig. 1) was useful in confirming and excluding adjacent organ involvement. Other workers have found this plane useful, particularly for lesions around the base or fundus of the bladder (Fisher *et al.*, 1985).

Both tests correctly predicted ureteric dilatation in all 9 patients. However, the state of the kidneys and ureters was already known from urographic or ultrasound findings. CT carries the advantage of showing hydronephrosis, if present, as well as routine information about the liver and para-aortic nodes. MRI at present is limited by time to the pelvis and hence ureteric dilatation is detected rather than hydronephrosis. With increasing MRI experience we are obtaining good abdominal images within the allotted time and future MRI may include full abdominal assessment. However, in this group of 9 patients the abdominal CT findings did not contribute to management; in no patient was para-aortic nodal enlargement demonstrated; although liver metastases were identified in the one patient whose disease was inoperable at EUA, routine liver function tests were markedly abnormal.

We hoped that MRI might identify early tumour involvement of fat beyond the bladder wall but because all of our patients showed some disturbance of fat planes from previous radiotherapy this hope was not substantiated. The concordance between the subjective grading of the pelvic fat planes on the CT and MRI images was reasonably precise but asymmetry of abnormal fat planes (which makes an infiltrative cause more likely) is more important than the severity of the change. In 3 of the 9 patients the tumour infiltrate was asymmetric, whereas in 4 patients the presumed radiotherapy effects were essentially symmetrical. However, in 2 patients tumour was found within extravesical fat despite seemingly symmetrical thickening of tissue planes.

The hope that MRI would be able to provide a recognisably different signal (especially on T_2 weighted images) in areas of extravesical infiltration compared with tissue merely affected by radiation change has not been substantiated. Formal T_2 measurements could not be performed as the volumes of abnormal tissue were very small, irregular and admixed with other structures, although this technique has been used for large confluent post-operative masses following excision of rectal tumours (Johnson *et al.*, 1987). However, a subjective assessment as to whether the area of abnormality was of greater signal intensity than neighbouring muscle on T_2 weighted images, a known feature of malignant processes (Ebner *et al.*, 1988), was attempted. This feature was not found in our patients with extravesical spread, presumably because the spread was of low volume and had occurred as an infiltrative process within fat rather than as a localised mass. Although the choice of pulse sequences in MRI is almost infinite, it seems unlikely that other sequences would have yielded different results. The pulse sequences used are in line with those employed at other centres and conform to the manufacturer's specifications for our machine.

Despite the advances in imaging, surgery remains the ultimate test as to whether cystectomy is possible in these patients. Nevertheless, CT and MRI can indicate those patients in whom it may prove difficult or impossible. Although both tests can detect adjacent organ involvement, neither can reliably identify early infiltration of paravesical tissues in these patients whose normal anatomy has been altered by previous radiotherapy.

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The Authors

A K Dixon, MD, MRCP, FRCR, Lecturer in Radiology, Honorary Consultant Radiologist.

A. M. Deane, FRCS, formerly Senior Registrar in Urology Now Consultant Surgeon, William Harvey Hospital, Ashford

P. T. Doyle, FRCS, Consultant Surgeon.

Requests for reprints to: A. K Dixon, University Department of Radiology, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ.

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Pathogenesis of Chronic Bacterial Prostatitis in an Animal Model

J. C. NICKEL, M. E. OLSON, A. BARABAS, H. BENEDIKTSSON, M. K. DASGUPTA and J. W. COSTERTON

Department of Urology, Queen's University, Kingston and Department of Biological Sciences, University of Calgary, Calgary, Canada

Summary—A reproducible rat model of chronic bacterial prostatitis was developed using a defined bacterial pathogen (*Escherichia coli*) to study the pathogenesis and persistence of chronic bacterial prostatitis. The progression of inflammation and its consequences from acute to chronic prostatitis were documented with microbiological, histological, ultrastructural and immunological data. Chronic bacterial prostatitis in this model was associated with sparse glycocalix-enclosed protected bacterial microcolonies within the prostatic acini and ducts which appeared to stimulate a persistent local and systemic immunological reaction resulting in chronic inflammation of the gland. This model has many striking similarities to the natural history of human chronic bacterial prostatitis.

Chronic bacterial prostatitis is probably the most common cuase of relapsing urinary tract infection in males (Meares, 1975) and few other ailments of the genitourinary tract cause more confusion for patients and clinicians than do the various prostatitis syndromes. Chronic bacterial prostatitis, perhaps the rarest of these syndromes, presents a very variable clinical picture and no findings on physical examination, rectal palpation of the prostate, cystoscopy or urography are specifically diagnostic of the condition, which can be confirmed only after culture of the urethra and bladder urine and expressed prostatic secretions (Meares and Stamey, 1968). This should differentiate between patients with chronic bacterial prostatitis, non-bacterial prostatitis, and prostatodynia; however, prior antibiotic treatment, poor diagnostic techniques and variable success rates (Pfau, 1986) cause further frustration for those involved in the management of this disease. The aetiology of the variable clinical response to treatment is thought to lie in the inability of the drug to penetrate into the prostate gland due to the specific pKa value of the antibiotic, lipid solubility of the drug, and the pH of the prostate gland (Winningham *et al.*, 1968; Madsen *et al.*, 1978; Sharer *et al.*, 1982). Available data imply, however, that many antimicrobial agents attain therapeutic levels in human prostatic interstitium and stroma (Fair *et al.*, 1979; Stamey *et al.*, 1980; Sharer *et al.*, 1982), suggesting that other mechanisms may allow bacterial persistence in the face of host defences and antibiotic therapy. An improved understanding of the local microbiological and immunological mechanisms involved in the pathogenesis of this complex disease process may be important. Immunological studes (Madsen *et al.*, 1983) have demonstrated a specific immunological response that may be associated with the aetiology and pathogenesis of chronic bacterial prostatitis. Very small numbers of bacteria that stimulate this prolonged immunological reaction may be protected from antibiotics by an intrinsic mechanism that they have evolved in response to unfavourable environments elsewhere (Costerton *et al.*, 1987). We have developed a reproducible rat model of chronic bacterial prostatitis, employing a defined bacterial pathogen (*Escherichia coli*), to study the pathogenesis and persistence of this disease.

Materials and Methods

Animal Model

Adult male Sprague-Dawley rats (weight 250–300 g) were obtained from an outbred colony of

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CRL: CD(SD)BR rats maintained at the University of Calgary. The rats were kept in polycarbonate box cages using corn cob bedding and were housed in quarters maintained at 20±2°C, 30±10% relative humidity and 12 h of daily illumination. They were provided with standard rat chow and tap water *ad libitum*.

A strain of *Escherichia coli* K-235 (01: KI: H$^-$) confirmed to be a successful rat urinary pathogen, was stored on brain heart infusion slants at −70°C and grown overnight in tryptic soy broth (TSB) in a 37°C shaker when required for inoculations. The cells were spun, washed 3 times and resuspended in TSB to give 10^8 cells/ml. The rats were anaesthetised with 4% halothane and the penile area was treated with 70% alcohol. The rats were subsequently catheterised with a lubricated sterile polyethelene tube (PE 10). We have demonstrated that a polyethylene tube of this diameter remains lodged in the proximal urethra and a fraction of methylene blue injected via this catheter enters the duct of the ventral prostatic gland. In this manner, 0.2 ml of the bacterial suspension containing 1×10^8 colony-forming units/ml was injected. Control rats were anaesthetised and catheterised in a similar fashion and 0.2 ml of sterile phosphate buffered saline (PBS) was injected via the catheter. The day of catheterisation was deisgnated Day 0. Rats were sacrificed by CO_2 intoxication on Days 1, 3, 7, and subsequently at weekly intervals, for at least 8 weeks. Urine was obtained from the intact bladder at the time of sacrifice by aspiration with a syringe and needle. The ventral prostate gland was removed and one-half was sonicated (15 min) in 10 ml PBS; 0.1 ml aliquots of urine and sonicated prostate underwent 10-fold serial dilutions from 10^{-2} to 10^{-5} and each dilution was spread-plated on McConkey agar plates. At the time of sacrifice, blood was aspirated for subsequent immunological studies.

Histological Studies

Random blocks of bladder and prostate from each group were prepared by fixation in 10% formalin solution. The samples were sectioned and stained with standard haematoxylin and eosin and examined under a light microscope.

Ultrastructural Study

These modified processing procedures for transmission electron microscopy (TEM) have been used successfully to examine the bacterial biofilm mode of growth in a number of chronic urinary tract infections (Nickel *et al.*, 1885a, b, c, 1987). At the time of autopsy, random sections of the prostate to be prepared for TEM were fixed in 5% glutaraldehyde in cacodylate buffer (0.1 M, pH 7.2) with 0.5% ruthenium red for 2 h at 22°C. The material was then washed 5 times in buffer, post-fixed in 2% osmium tetroxide in buffer, washed 5 more times in the buffer and dehydrated through a series of acetone washes. All of the solutions used in processing the specimen, from the washes after glutaraldehyde fixation to dehydration with 70% acetone solution, contained 0.05% ruthenium red. After further dehydration in propylene oxide, the specimen was embedded in Spurr low viscosity embedding resin (Spurr, 1969), sectioned, stained with uranyl acetate and lead citrate (Reynolds, 1963), reinforced with evaporated carbon and examined with a Hitachi 600 transmission electron microscope at an acceleration voltage of 60 kV.

Immunological Studies

E. coli strain K-235 (0.1: K.1: H$^-$) according to the international antigen typing scheme was used as the standard strain for the antigen preparation and the prostate infection of rats. Antigens were prepared by the method of Hoiby and Axelsen (1973) with slight modifications. Crossed immunoelectrophoresis was performed using an intermediate gel for all of the studies. The intermediate gel contained either serum, antigen (for crossed line immunoelectrophoresis) or saline (0.145 M) as a control. All immunoelectrophoresis techniques were performed according to published procedures (Lam *et al.*, 1983) with slight modifications. Circulating immune complexes were studied in the serum using a CIC Raji cell radioimmune assay (Dasgupta *et al.*, 1987). Results were expressed as the number of SD units above the normal (control) mean; values greater than 2 SD were considered postive (Dasgupta *et al.*, 1982).

Immunofluorescent studies of sections of the prostate gland were undertaken to determine whether immunoglobulins lodge within the prostate gland around unresolved bacterial microcolonies. Direct immunohistological methods were used at both the light and electron microscopic levels (Cornish *et al.*, 1984).

Results

Seventy-five rats were used in the study (10 controls, 65 test rats). Four rats in the test group died of overwhelming infection presumed secondary to acute prostatitis and/or urosepsis. Table 1 shows the microbiological data of rats sacrificed during

Table 1 Microbiological Data

Time (days)	*No. of rats killed*	*No. of rats infected*	*Infection rate (%)*	*Mean LOG CFU/g of infected prostates*	*SD*
1	6	6	100	8.618	0.707
3	5	5	100	8.519	0.567
7	6	4	67	6.113	0.750
14	6	3	50	7.488	0.984
21	3	2	67	5.827	0.952
28	8	8	100	6.859	1.292
35	7	5	71	7.489	2.545
42	7	3	43	5.510	1.309
49	7	3	43	7.086	1.818
56	6	3	50	5.311	1.463

the study period. All developed acute prostatis in the first 3 days after bacterial inoculation of the prostate. At this stage the bacterial colony-forming unit (CFU) count was very high. After the first week and during the following 7 weeks, approximately 50% of the rats spontaneously cleared the bacterial infection and did not develop chronic prostatitis. The rats with acute prostatitis that were unable to clear the infection developed a microbiologically proven chronic postatitis that was sustained over the 8 weeks of the study.

At the time of autopsy the ventral prostate glands of animals with acute prostatitis (Days 1–14) were swollen, congested, oedematous and hyperaemic. The surrounding tissues were extremely oedematous. On cut section, areas of inspissation were surrounded by normal prostatic tissue. Other accessory glands and the bladder were normal in gross appearance. As the infection became chronic (Days 21–56) the ventral prostates began to shrink (up to about one-quarter their normal size) and became firm with a yellowish-brown colouration. On cut section they grossly demonstrated a uniform firm yellowish tissue surface without exudate. The surrounding adipose tissue, connective tissue and accessory glands were normal in appearance.

Histopathological examination of the prostate during the initial acute infection stage (Days 1–14) demonstrated an acute response to the bacterial challenge with severe infiltration of polymorphonuclear cells into bacteria-containing spaces (Fig. 1). The acini that had a severe cellular infiltration were often adjacent to acini with little or no inflammatory response. The adipose and connective tissue surrounding the gland was extremely oedematous and congested. The accessory glands were histologically normal and only occasionally was there any pathological evidence of cystitis. As the infection became chronic, fibrous tissue proliferation and acinar regression occurred and some acinar and interstitial spaces became heavily infiltrated with lymphocytes (Fig. 2). This lymphocyte and fibrous tissue response completely engulfed the prostate gland, so that it consisted only of fibrous tissue with multifocal areas of lymphocyte infiltration.

Ultrastructural examination of the ventral postate in rats with chronic prostatitis demonstrated a sparse bacterial presence within the gland, even though homogenation of the gland itself confirmed bacteria to be present. However, when the bacteria

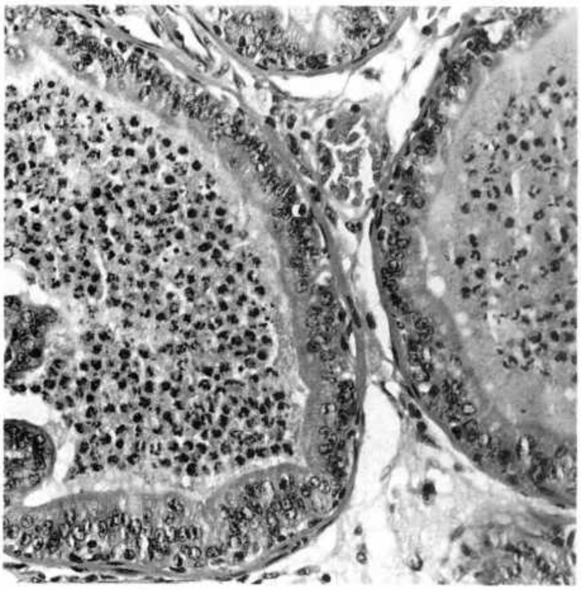

Fig. 1 Histological section of prostate showing stromal oedema and marked distension of prostatic acini due to massive polymorphonuclear leukocyte infiltration. This infiltration broke focally through the acinar basement membrane to form stromal microabscesses. In some glands normal uninvolved acini were seen next to heavily inflamed ones. (H and E × 1000).

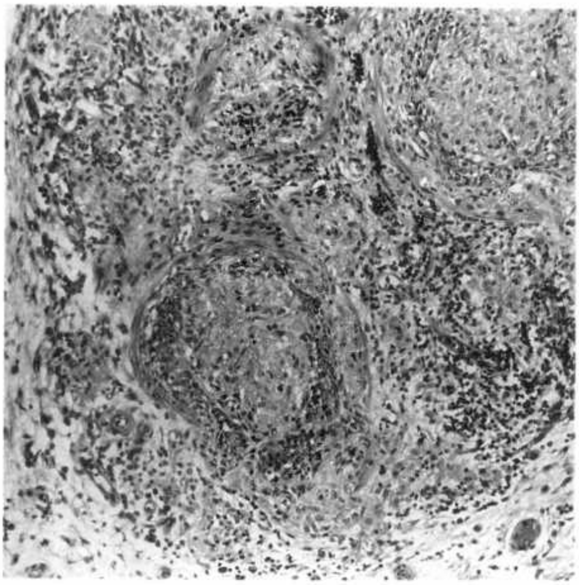

Fig. 2 As the process advanced into the chronic stage, the acini underwent progressive obliterative changes, characterised by proliferation of fibroblasts and histiocytes within the acinar basement membrane and atrophy of the epithelium. This was accompanied by lymphocyte infiltration in the interstitium and within acini, with occasional germinal centres. Fibrosis became more pronounced and led to an end-stage fibrous scarring of the entire gland. In some specimens, however, segments of the glands showed end-stage fibrosis while other segments were comparatively normal. (H and E × 500).

were discovered within the prostate gland, they were localised to microcolonies within the prostatic acini rather than the interstitium (Fig. 3) and these bacteria were present in a glycocalix-enclosed microcolonial mode of growth (Fig. 4). This glycocalix was highly hydrated and composed primarily of exopolysaccharide. In Figure 4 it is seen to be severely condensed and dehydrated, but in its hydrated state it would have constituted the bacterial colonies' functional matrix. The bacterial microcolonies appeared to be firmly adherent to the ductal and acinar mucosal layer (Fig. 5). This was mediated in part by the bacterial biofilm's glycocalix, which was also probably responsible for a significant part of the intense immune stimulation provoked by these bacteria.

Crossed immunoelectrophoresis (XIE) of serum, obtained at the time of sacrifice from rats that developed acute prostatitis, rats that were able to clear their acute prostatic infection spontaneously, and rats that developed a persistent chronic prostatitis, demonstrated characteristic patterns. During the first 3 days of the acute prostatitis stage a serum immune reaction to the antigenic cell surface components of *Escherichia coli* K-235 could not be demonstrated. Rats that developed a spontaneous cure of their prostatic infection within

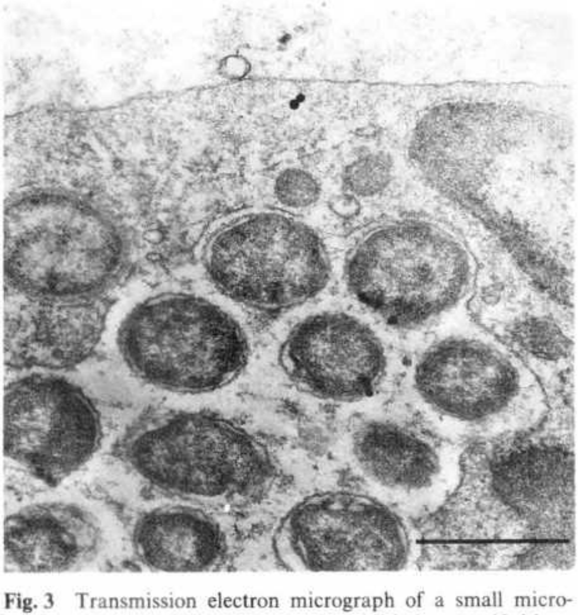

Fig. 3 Transmission electron micrograph of a small microcolony of *E. coli* within the prostatic acini being engulfed by a polymorphonuclear cell. Bar = 1 μm.

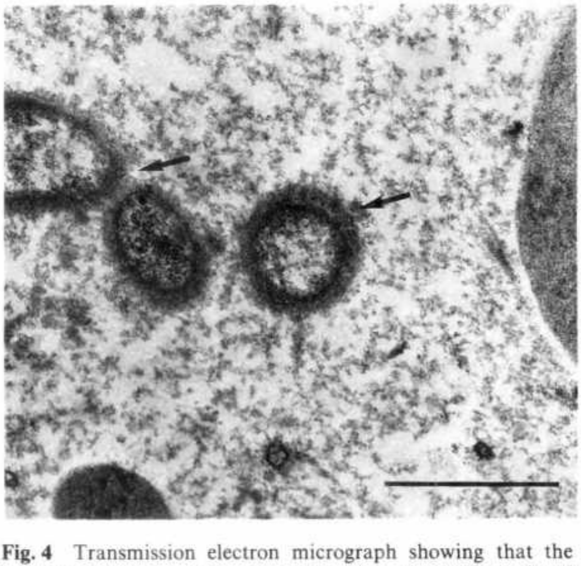

Fig. 4 Transmission electron micrograph showing that the bacteria within the acini were present in a glycocalix-enclosed microcolonial mode of growth. This glycocalix (arrow) in its hydrated state would have composed the bacterial microcolony's functional matrix and is responsible for protecting the enclosed bacteria, mediating its attachment to surfaces and provoking a strong immunological stimulation. Bar = 1 μm.

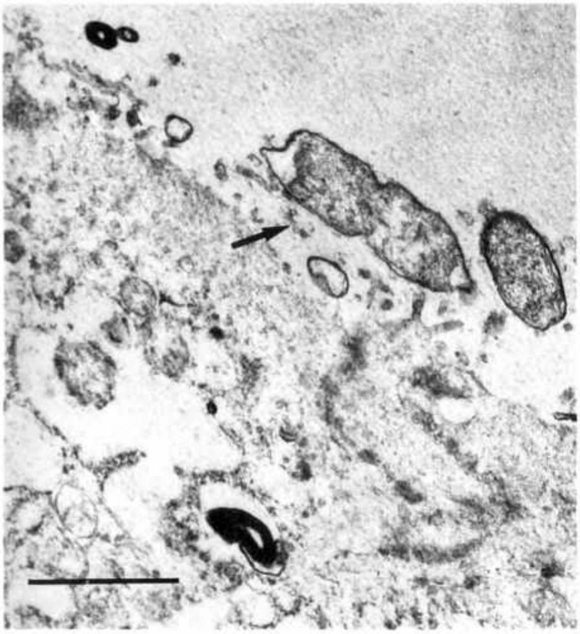

Fig. 5 Transmission electron micrograph showing the bacterial biofilm firmly adherent to the ductal and acinar mucosal layer. This adhesion is mediated in part by the extracellular glycocalix material secreted by the adherent bacteria within their microcolony. In these preparations the glycocalix material is condensed down to the reticular material (arrow). Bar = 1 μm.

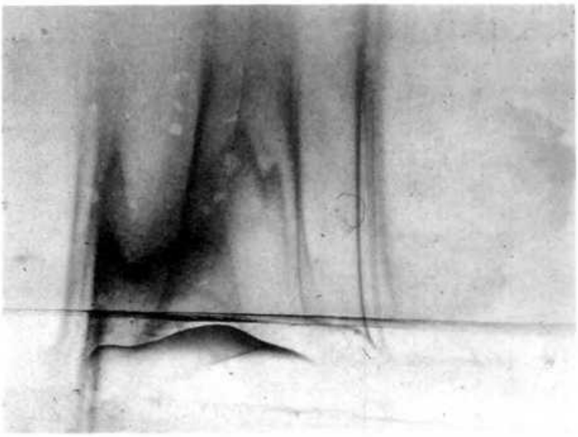

Fig. 6 Crossed immunoelectrophoresis of serum from rats with chronic prostatitis showing an intense immune reaction associated with the immunological components produced by *Escherichia coli* K-235.

7 days had a similar non-reaction on XIE. Rats that had sustained bacterial growth in the prostate gland at 7 days were seen to provoke a weak antibody response associated with the specific *E. coli* used in the initial prostatic inoculation. Rats that were sacrified after Day 14, and which demonstrated no bacterial infection on culture of homogenised prostatic tissue (Table 1), demonstrated either no immune response, which probably meant that they had eradicated the bacterial infection within the first week following inoculation, or a weak antibody response, which may signify a later spontaneous cure of the prostatic infection. Crossed immunoelectrophoresis of serum from rats that had sustained low grade bacterial infection of the prostate (chronic postatitis) at Day 56 showed an intense serum immune reaction associated with the immunological components produced by *Escherichia coli* K-235 (Fig. 6). Control rats showed no demonstrable serum immune immunological changes on XIE. Employing a Raji cell radioimmune assay, circulating antigen-antibody complexes were found within the serum of the 3 rats with confirmed chronic prostatitis at Day 56.

The immunohistopathological data are presented in Table 2. Immunoglobulins were not detectable in the ventral prostate glands of control rats. IgM was detected on the basement membrane of some acini on Day 7. As in the histopathology, there were normal areas adjacent to areas with marked fluorescence, indicating only localised infection within the prostate. After 14 days, both IgG and IgM could be detected on the acinar basement membrane, within inflammatory cells and within the surrounding connective tissue (Fig. 7). As the infection became more chronic, acinar architecture was destroyed and the immunoglobulins were detected within inflammatory cells and surrounding connective tissue. No immunoglobulins were detected in prostate glands in which bacterial presence was not confirmed.

Table 2 Immunohistopathological Data

Time (days)	*No.*	*IgG Positive*	*IgM Postive*
0	4	0	0
7	4	0	4
14	4	2	3
21	4	2	3
28	4	3	3
35	4	2	2
42	4	3	2
49	3	3	3
56	3	1	2
	34	14	19

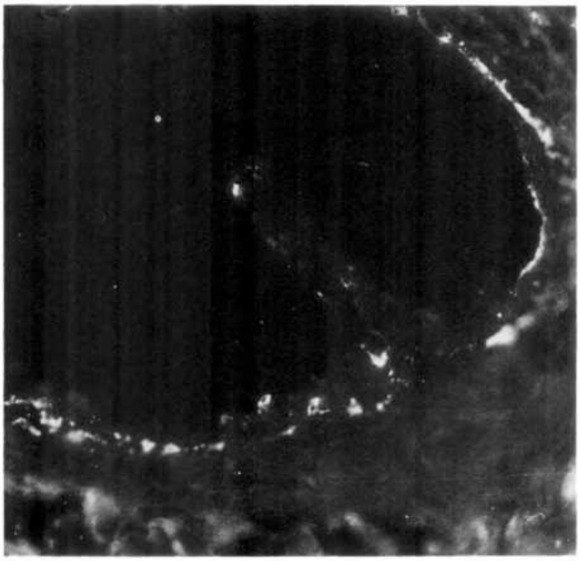

Fig. 7 Immunofluorescent IgG staining of acinar basement membrane of rat with chronic prostatitis (Day 35). (×640).

Discussion

Over the last 2 decades, work on human prostatitis has been limited to localisation studies (Meares and Stamey, 1968; Meares, 1975; Pfau, 1986), antibiotic diffusion studies in dogs (Winningham *et al.*, 1968; Madsen *et al.*, 1978; Sharer and Fair, 1982) and evaluation of antibiotic treatment (Meares, 1975; Fair *et al.*, 1979; Stamey, 1980). Except for the diffusion experiments in animals, which may not be an accurate reflection of antibiotic penetration into the prostate in human prostatitis, little work has been done on the pathogenesis, aetiology and reasons for bacterial persistence within the prostate. The question of why such a debilitating, diffuse, chronic inflammatory disease process can occur and persist, even with seemingly adequate therapy and despite the relative scarcity of bacteria within the gland, has not been fully investigated. Immunological studies have been primarily concerned with using immunological techniques for the diagnosis of prostatitis and defence mechanisms present in the disease, rather than a study of the immunological mechanisms that may be involved in the actual disease process itself. Many workers have found significantly increased levels of IgG, IgA and IgM in the prostatic secretions of patients with unresolved prostatitis compared with controls (Chodirker and Thomasi, 1963; Ablin *et al.*, 1971; Gray *et al.*, 1974; Fowler and Mariano, 1984; Shortliffe and Wehner, 1986). Others have demonstrated antigen-specific antibody coating of bacteria isolated from the lower urinary tracts of patients with prostatitis syndromes (Thomes *et al.*, 1974; Riedasch *et al.*, 1977). Patients with chronic *E. coli* prostatitis may have elevated serum antibody titres against their prostatic pathogens (Meares, 1977). A cure of chronic *E. coli* prostatitis results in a return to normal of elevated serum antibody and prostatic antibody titres. The clinical implications drawn from the present study on the development of chronic bacterial prostatitis is limited by the differences in anatomy and physiology encountered in all animal modelling of human disease. The findings, however, suggest that in chronic prostatitis the bacteria, although scarce, are found in glycocalix-enclosed microcolonies within the prostate. We have previously shown that bacterial growth within glycocalix-enclosed biofilms on an inert surface protects the bacteria from the effects of antibiotics (Nickel *et al.*, 1985c). We have also shown that bacteria associated with struvite stone calculogenesis were resistant to antibiotic therapy because of this protective mode of growth (Nickel *et al.*, 1987); it is possible that the bacteria may be closely associated with corpora amylacea or prostatic calculi. We have studied this mode of bacterial growth in other natural and infective systems and feel that the process has evolved ecologically to protect bacteria from a harmful environment (Colsterton *et al.*, 1987). Similar bacterial microcolonies within the prostate may be partially protected from host defences and antibiotics. Our study confirms a vigorous local and systemic immune response to bacterial persistence within the prostate gland. The systemic and local immune response against the exopolysaccharide and the surrounding glycocalix material produced by these bacteria may set in motion an immunological process that may be involved in the pathogenesis of the disease itself manifested by the histopathological changes demonstrated.

This animal model has many striking similarities to the development and persistence of human chronic bacterial prostatitis and suggests a scenario for the natural history of the disease. It seems reasonable to assume that the bacteria become lodged in the prostate from adjacent urethritis or reflux of infected urine into the prostatic ducts (Meares, 1986). In our study, bacteria entered the prostate from retrograde injection via the prostatic duct, causing acute (clinically evident) or subacute (not clinically evident) prostatitis. At this stage, the bacteria within the prostate are either eradicated because of the non-specific defences in the prostate (mechanical factors, antimicrobial substances and prostate secretions), specific humoral defences (serological, local) or aggressive antibiotic therapy. However, in some cases the bacteria are not eradicated because of inadequate levels of antibiotics in the prostate, suppressed defence mechanisms or increased bacterial virulence and they form patchy areas of bacterial colonisation within the prostatic ducts or acini. These microcolonies produce an extensive exopolysaccharide glycocalix matrix. Direct observation of bacteria in natural pathogenic ecosystems has demonstrated that most bacteria, especially in a threatening enivronment, grow in sessile matrix-enclosed biofilms (Costerton *et al.*, 1987) and are thus relatively protected against host defences as well as antibiotic therapy. A much smaller number of planktonic bacterial cells are periodically released from such biofilms in pathogenic systems; in this instance, they would be released into the prostatic ducts. These would be the bacteria cultured in the simultaneous quantitative bacterial culture techniques of Meares and Stamey (1968). During acute flare-ups of chronic prostatitis the bacteria within the prostate may multiply and present a picture similar to that of acute prostatitis with a generalised bacterial presence within the entire prostate gland as well as cystitis. At this stage, bacterial cultures of prostatic secretion and mid-stream voiding specimens would be more likely to be positive and subsequent antibiotic therapy most successful. Clinical experience confirms that the best success rates are obtained when the bacterial pathogen is confirmed on quantitiative culture (Meares, 1975; Stamey, 1980; Meares, 1986; Pfau, 1986). The immune system recognises not the bacterial cell but the exopolysaccharide matrix or glycocalix, as well as extracellular products such as LPS (lipopolysaccharides), endotoxins, *etc*, of these biofilms. These result in elevated specific antibody titres against the surface capsular structures of the offending organism. These circulating antibodies deposit on the acinar basement membrane and within the surrounding connective tissue matrix. Circulating immune complexes can be found and this attests to the chronic nature of the immunological process. This may account for the generalised chronic inflammation seen within the interstitium of the prostate despite the relative rarity of any bacteria nearby. A similar mechanism is now believed to be involved in other chronic bacterial infections such as the chronic low grade pneumonia of cystic fibrosis (Dasgupta *et al.*, 1987). Future studies employing immune modulation or manipulation in this animal model may help us to delineate further the role of the immune system in the pathogenesis of this chronic infective disease.

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The Authors

J. C Nickel, MD, FRCS(C), Associate Professor, Department of Urology, Queen's University.

M. E Olsen, DVM, Associate Professor, Department of Biological Sciences, University of Calgary.

A. Barabas, DVM, Associate Professor, Faculty of Medicine, University of Calgary

H Benediktsson, MD, Associate Professor, Faculty of Medicine, University of Calgary.

M. K. Dasgupta, MD, Associate Professor, Faculty of Medicine, University of Calgary.

J. W Costerton, PhD, Professor, Department of Biological Sciences, University of Calgary.

Requests for reprints to · J C. Nickel, Department of Urology, Queen's University, Kingston, Ontario, K7L 2V7, Canada.

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Controlled Study of Cimetidine in the Treatment of Benign Prostatic Hypertrophy

A. LINDNER, J. RAMON and M. E. BROOKS

Departments of Urology and Rehabilitation, Sheba Medical Center, Tel Hashomer, Israel

Summary—A series of 60 patients with benign prostatic hypertrophy (BPH) was randomly divided into 2 groups; 30 received cimetidine 1 g/day for 4 weeks and 30 received vitamin C 1 g/day for the same period. The study was double-blind. No significant difference between the 2 groups was observed in mean urinary flow, subjective obstructive or irritative symptoms, or prostate size. There was a statistically significant difference in the peak urinary flow rate but this was a result of net deterioration in the control group. Cimetidine was found to be no more active than vitamin C in treating benign prostatic hypertrophy.

Cimetidine, a histamine H_2-receptor antagonist, is widely used in the treatment of peptic ulcer, reflux oesophagitis and the Zollinger-Ellison syndrome. Early toxicology studies with cimetidine in rats and dogs showed a decrease in prostate and seminal vesicle weights, suggesting the presence of antiandrogenic activity (Leslie and Walker, 1977). Winters *et al.* (1979) confirmed these studies in rats. They found that cimetidine showed antiandrogenic activity at the cell receptor level. It competitively inhibited dihydrotestosterone (DHT) binding to its cytoplasmic receptor and lowered the specific nuclear uptake of (3H) dihydrotestosterone in rat prostate slices.

In man, cimetidine has been associated with gynaecomastia, a property associated with other antiandrogenic drugs. There are reports of sexual inhibition, loss of libido and impaired sexual performance (Peden *et al.*, 1979) and reports indicating reduction in sperm count in patients treated with cimetidine (Van Thiel *et al.*, 1979).

Since androgens have been recognised as necessary for the development and maintenance of BPH, this study was undertaken to assess the potential of cimetidine as a therapeutic agent.

Patients and Methods

The study group included 60 patients, aged 43 to 70 years (mean 61.5), affected by BPH as diagnosed on the basis of clinical history, rectal examination and intravenous urography. Patients above the age of 70, those with diabetes mellitus or urinary infection, and patients under treatment with other drugs for BPH were excluded from the trial.

They were randomly divided into 2 groups. One group was treated with vitamin C 1g/day orally for 4 weeks and served as a control group. The experimental group received cimetidine 1 g/day orally over the same period. The study was double-blind. Changes in subjective symptoms, urine flow rates and prostate size were documented.

The subjective symptoms were divided into 2 categories and graded by a numerical score. The obstructive symptom score was derived from the symptoms of hesitancy, terminal dribbling and the quality of the urinary stream.

The obstructive symptoms were graded as follows:

(1) Quality of stream: normal (0 points), variable (1), weak (2), dribbling (3).
(2) Hesitancy: no (0 points), yes (1).
(3) Terminal dribbling: no (0 points), variable (1), yes (2).

The maximum obtainable obstructive symptom score was 6 points.

The irritative symptom score was derived from the symptoms of dysuria, urgency, frequency and

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nocturia. The irritative symptoms were graded as follows:

(1) Dysuria: no (0 points), yes (1).
(2) Urgency: none (0 points), mild (1), moderate (2), incontinence (3).
(3) Frequency: >3 h (0 points), every 2–3 h (1), every 1–2 h (2), <1 h (3).
(4) Nocturia: 0–1 (0 points), 2–3 (1), 4–5 (2), >5 (3).

The maximum obtainable irritative symptom score was 10 points.

The total subjective symptom score was the sum of the obstructive and irritative scores. A change of more than 2 points in the subjective symptom score was considered statistically significant.

The size of the prostate was assessed on rectal examination by 2 urologists. Urine flow was measured using a Life-Tech model 1003A uroflowmeter. Flow rates were reported as peak and mean flows in ml/s. Each patient was examined at the onset of the study and on day 29. Statistical analyses were by Student's *t* test and paired *t* tests.

Results

A total of 51 patients completed the trial—26 from the cimetidine group and 25 from the control group.

Only 9 patients failed to complete the trial. In 3 cases treatment was discontinued because of adverse gastrointestinal effects (nausea and/or abdominal pain), 1 from the study group and 2 from the control group. Another 2 patients were removed from the study group by their family doctor because of chest pain. One patient from the control group withdrew following a deterioration in his urinary symptoms. The remaining 3 patients (1 from the study group and 2 from the control group) withdrew from the trial without explanation.

The total subjective symptom score improved significantly (at least 2 points) in 8 patients (31%) in the treated group. In 3 of these patients the improvement was observed mainly in the obstructive symptoms. In the remaining 5, the improvement was primarily in the irritative symptoms. A significant improvement was also found in 8 control patients (32%). In 3 of these patients improvement was primarily observed in the obstructive symptoms and in 3 others primarily in the irritative symptoms. No deterioration in the total subjective symptom score was recorded in any patient during the study.

The Table shows the value of the total subjective symptom score, the obstructive and irritative scores and the urodynamic findings, before and after treatment.

The mean total subjective symptom score in the cimetidine group improved by 1.3 points (0.4 points obstructive and 0.9 irritative) and the mean total subjective symptom score in the control group improved by 1.1 point (0.6 obstructive and 0.5 irritative). These results are summarised in the Table.

The improvement in the mean total subjective symptom score in both groups was therefore less than the 2 points defined as a significant change in each group and the difference between the 2 groups was not statistically significant.

The peak urine flow rate in the cimetidine group improved in 14 patients (54%) and 4 showed an improvement of more than 5 ml/s. A deterioration was observed in 7 patients (27%), with 3 exhibiting a decrease of more than 5 ml/s. Overall, the average peak flow rate improved by 1.12 ml/s in the group treated with cimetidine.

In the control group, the peak flow rate improved in 8 patients (32%); only 2 demonstrated an improvement of more than 5 ml/s. A deterioration was observed in 14 patients (56%). In 6 of these the decline was greater than 5 ml/s. The average peak flow rate in the control group deteriorated by 3.0 ml/s. The net deterioration in peak urine flow in the control group represents the only statistically significant difference (<0.05) between it and the cimetidine group.

Table Results of Symptom Analysis and Urodynamic Examinations

	Before treatment (mean)		*After treatment (mean)*	
	Cimetidine	*Control*	*Cimetidine*	*Control*
Total symptom score	7.12	7.04	5.84	5.88
Obstructive score	3.81	4.40	3.42	3.80
Irritative score	3.31	2.64	2.42	2.08
Peak flow rate (ml/s)	7.96	12.67	9.08	9.67
Mean flow rate (ml/s)	2.97	4.08	3.71	4.33

In the cimetidine group, mean urine flow improved in 14 patients (54%) and deteriorated in 9 (35%). In the control group, 9 patients (36%) showed improvement, while deterioration was observed in 14 (56%). The mean flow rate in the cimetidine group improved by 0.74 ml/s, while in the control group it deteriorated by 0.25 ml/s. This difference was not statistically significant. No change in the size of the prostate, as measured by rectal palpation, was noted in either group.

Discussion

The occurrence and progression of BPH with advancing age suggests a correlation between the disease and changes in the endocrine milieu associated with ageing. Androgen deprivation causes a reduction in the size of the prostate, relieving urinary obstruction due to BPH. Androgen deprivation may be achieved by castration (Huggins and Stevens, 1940), by the administration of oestrogens or antiandrogenic drugs.

Cyproterone acetate, an antiandrogen that blocks the androgen receptors (Scott and Wade, 1969), was found to be effective in relieving the symptoms associated with BPH. Unfortunately, its use is limited due to severe side effects. Megestrol acetate (Geller *et al.*, 1979) blocks androgen action by reducing the activity of intracellular 5 reductase. Some investigators have reported that administration of this drug induces a decrease in prostate size and an improvement in urine flow rates in patients with BPH (Geller *et al.*, 1979), while others have found the changes in urine flow rates to be minimal (Donkervoort, 1983). Endocrine manipulation in patients with BPH, using other drugs such as medrogestone, flutamide, amphotericin B and candicidin, failed to produce any significant improvement in prostate size or urinary symptoms.

Cimetidine expresses an antiandrogenic activity by competitive binding to the cellular receptor for DHT (Winters *et al.*, 1979), suggesting that it might evoke a prophylactic response in patients suffering from BPH. This study was therefore designed to evaluate the effect of cimetidine on urinary symptoms, prostate size and urine flow rate in patients with BPH; 31% of those receiving cimetidine and 32% of those in the control group demonstrated an improvement in symptoms. A positive response to placebo is common in patients with BPH (Castro, 1972), so that the improvement in the treated group appears to be no more than a placebo effect.

An increase in the peak flow rate was noted in 54% of patients treated with cimetidine and in 32% of the controls. Although this difference was statistically significant, the improvement in the peak flow rate had no clinical expression. Nevertheless, this improvement in the treated group may suggest that cimetidine has a limited effect on BPH patients. No difference was observed between the groups with respect to average mean flow rate and there was no change in prostate size in either group.

The incidence of antiandrogenic side effects in patients with peptic disease treated with cimetidine was low and was particularly evident in patients on high doses and long-term treatment.

We used a low dose regime for a short period of time. Under these circumstances, cimetidine did not prove to be a useful drug in the treatment of BPH.

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The Authors

A. Lindner, MD, Head, Department of Urology, Edith Wolfson Medical Center

J. Ramon, MD, Resident, Department of Urology, Sheba Medical Center

M. E. Brooks, MD, Consultant, Department of Rehabilitation, Sheba Medical Center.

Requests for reprints to: A. Lindner, Department of Urology, Edith Wolfson Medical Center, P O Box 5, 58100 Holon, Israel

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Permanently Implanted Urethral Stent for Prostatic Obstruction in the Unfit Patient

Preliminary Report

C. R. CHAPPLE, E. J. G. MILROY and D. RICKARDS

Departments of Urology and Radiology, Middlesex Hospital, London

Summary—We describe the use of a new urethral stent implanted into 12 patients with prostatic outflow obstruction. All were in a high risk group for surgery and 11 were treated successfully, with a follow-up of 1 to 11 months (median 9). The majority of patients were satisfied with the procedure, which provided a quick, safe and effective alternative to conventional surgical treatment. The stent, woven from fine stainless steel in the form of a tubular mesh, was inserted via a delivery device using combined ultrasound and endoscopic control under local anaesthesia. The procedure was well tolerated, the stent becoming covered with epithelium by 6 to 8 months following insertion, yet allowing easy removal within the first 4 to 6 weeks should the need arise. This technique provides a useful alternative to conventional surgical treatment in the high risk patient.

Prostate obstruction is the single commonest cause of male urological symptoms. Surgical removal of obstructing prostatic tissue has been in widespread use for over 50 years and remains the principal therapeutic choice. In recent years it has been increasingly recognised that conventional surgery is not without its dangers (Roos *et al.*, 1989), particularly in the elderly, unfit patient. A number of alternative, minimally invasive therapeutic options have been explored in recent years (Chisholm, 1989), but none of these has so far been as effective. This is of particular importance in the elderly, infirm patient who may not be able to comply with or tolerate pharmacological therapy and where the only previous alternative has been long-term catheter drainage. We have recently reported the use of a new urethral stent ("Wallstent"; Medinvent SA, Lausanne, Switzerland) for implantation into the strictured urethra (Milroy *et al.*, 1988, 1989a). Previous experience of its use in over 50 patients with complex urethral strictures over a follow-up period of up to 2 years has confirmed the efficacy of this treatment. This report describes our preliminary experience with its implantation into the prostate.

Patients and Methods

Since conventional surgical prostatectomy is the most effective therapeutic option available for the treatment of prostatic outflow obstruction, this study was from the outset designed for patients with severe cardiorespiratory disease or other intercurrent pathology which rendered conventional surgery either hazardous or inappropriate. Twelve such patients entered this study with full informed consent (Table); 7 were in an extremely high risk group because of intercurrent disease; of the remaining 5 patients, 3 had coexisting disseminated malignant disease, 1 had severe cardiovascular disease with atherosclerotic dementia and 1 had respiratory disease and bilateral Girdlestone arthrodeses. Eight patients presented with acute retention of urine, 1 with chronic retention and 3 with severe symptoms of outflow obstruction; all of the patients in retention had failed at least one trial

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Read at the 45th Annual Meeting of the British Association of Urological Surgeons in St Helier, June 1989.

Table Details of Patients

Patient	*Age (years)*	*Presenting complaint*	*Co-existing medical history*	*Peak urine flow rate (ml/s) (All volumes > 120 ml)*		*Bladder residual volume (ml)*	*Follow-up (months)*	*Outcome*
				Pre-op.	*Post-op.*			
G McC.	70	AR	COAD, Bilateral fixed hips	—	13.1	20	9	Good position, full epithelial cover
J.B.	78	AR	Disseminated carcinoma prostate, severe myocardial ischaemia, COAD	—	40.0	<100	9	Declined cystoscopy, no other problems
J.M.	69	AR	Adenocarcinoma larynx, disseminated adenocarcinoma kidney	—	13.8	0	11	Full epithelial cover*, 2 mm protrusion into bladder
S.S.	72	AR	Adenocarcinoma bronchus, COAD	—	13.6	0	8	2 mm protrusion into bladder with slight calcification, 90% epithelial cover
L.R.	84	CR	Severe atherosclerotic disease, dementia	—	patient unable to co-operate; good on screening	0	1	Post mortem, early epithelisation, 1 mm protrusion into bladder (patient died of bronchopneumonia)
M.S.	75	AR	Myocardial ischaemia, depression	—	9.6	0	9	Good position, full epithelial cover
G H.	72	AR	Severe myocardial ischaemia	—	6.8	0	9	2 stents, complete cover, 2 mm protrusion into bladder*
A B.	78	PO	Bilateral hip prosthesis, COAD, neck fusion	11.1	17.7	70	11	Full epithelial cover, 4 mm stent protruding into bladder*
H.M.	78	PO	Pacemaker, CABG × 3 aortic valve	4	18.1	0	7	80% cover, 1 mm stent protruding into bladder, slight calcification on stent protruding into bladder
M.K	65	AR	Previous MI, angina, COAD	—	15.9	50	7	70% epithelial cover, 4 mm protrusion of stent into bladder. Patient died of further MI
N.H.	70	AR	COAD, angina	—	12.0	50	7	Good position, complete epithelial cover
S S.	67	PO	CABG, unstable angina	18	15.6	0	10	Severe frequency and residual detrusor instability, full epithelial cover of stent, good position

AR = Acute retention.
CR = Chronic retention.
PO = Severe symptoms of prostate obstruction.
* = Stent protuding into bladder not fully covered.
COAD = Chronic obstructive airways disease
CABG = Coronary artery bypass graft

without catheter combined with adrenergic blockade.

All patients underwent routine clinical examination and subsequent investigations included routine biochemistry, serum acid phosphatase and prostate specific antigen, ultrasound of the kidneys, transrectal prostatic ultrasound and urodynamic investigation. Patients with obstructive uropathy were excluded from the study. Eleven had benign prostatic enlargement as defined by clinical examination, transrectal ultrasound scanning and normal serum markers. One patient had disseminated carcinoma of the prostate. Their mean age was 72.8 ± 1.59 years (range 65–84). Individual case histories are detailed in the Table.

The stent was introduced using the delivery system described by Milroy *et al.* (1989b). In all cases local anaesthetic jelly was inserted into the urethra with the concurrent use of an intravenous benzodiazepine to provide sedation. The patients were placed in the left lateral position and a linear array transrectal ultrasound probe inserted *per rectum*. A flexible cystoscopy was carried out to exclude bladder tumours and stones and to confirm the position of the bladder neck and distal sphincter mechanism on the ultrasound pictures (Fig. 1). The distance between the bladder neck and sphincter mechanism was then measured. A guidewire was passed into the bladder and the flexible cystoscope withdrawn. The stent is available in varying sizes, the length chosen depending on the distance between the bladder neck and distal sphincter mechanism on the ultrasound image. A mesh prosthesis of appropriate length, constrained in its compressed form on the delivery catheter, was then passed over the guidewire. The stent was initially positioned with its proximal end just within the bladder and the delivery catheter was then pressurised with normal saline through a side arm to 3 atmospheres to separate the 2 layers of the plastic membrane holding the stent in its compressed state. The outer layer of the plastic membrane was withdrawn approximately 2 cm, thereby enabling the proximal end of the stent to open, and further opening of the prosthesis was arrested by depressurising the apparatus. The stent was then cautiously withdrawn over the guidewire, allowing its partially open proximal end to be accurately positioned at the bladder neck, under ultrasound control. This partial opening of the stent allowed it to grip the tissues of the bladder neck and thus provide anchorage. When the operator was satisfied with the position of the stent, the membranes were repressurised and the outer sheath was fully withdrawn, allowing full release of the stent. The delivery catheter was then removed. The unconstrained calibre of the stents was 14 mm. If the stent did not open to 12 mm diameter during this procedure, balloon dilatation was carried out using a 12 mm diameter balloon passed over the guidewire. The position of the stent was then confirmed endoscopically using the flexible cystoscope (Fig. 2A). In all patients prophylatic antibiotic cover was continued for 48 h; 3 patients required suprapubic catheter drainage for 48 h.

Patients were reviewed regularly with urine cultures and urine flow rates. The effectiveness of the treatment and positioning of the stent was assessed by urodynamic investigation, urethroscopy (Fig. 2B) and urethrography (Fig. 3). Transrectal ultrasound scan of the prostate was carried out 2, 4 and 6 months following the procedure.

Results

Two stents were removed, without difficulty, before full release from the covering membrane because of poor positioning and a second stent was successfully placed. Five stents required balloon dilatation to open them fully and 1 patient required 2 stents to cover the prostate completely, an inadequate length of stent having been used initially (one of the earliest patients treated). The internal diameter of the implanted stent was large enough to permit subsequent endoscopic examination and transurethral surgery of the bladder if necessary.

Since 9 of the 12 patients presented with urinary retention, voiding parameters were not available at entry to the study. The results of urodynamic investigation following stent insertion are detailed in the Table. Eleven patients were fully satisfied with the results of this procedure and all were passing urine at the time of review. This is at first sight a surprising finding in a group which includes so many patients who presented in retention, but it must be remembered that this was a select group, since all patients with poor detrusor function were excluded. The mean follow-up period for these patients following stent insertion was 8.2 ± 0.77 months (range 1–11). Only 1 patient (S.S.) is unhappy with the result of this therapy because of persistent frequency, which has been demonstrated on urodynamic examination to be associated with severe persistent detrusor instability. The patient with atherosclerotic disease and associated dementia (L.R.) died of bronchial pneumonia 1 month after insertion of the stent. Post mortem examination confirmed that the stent had been placed

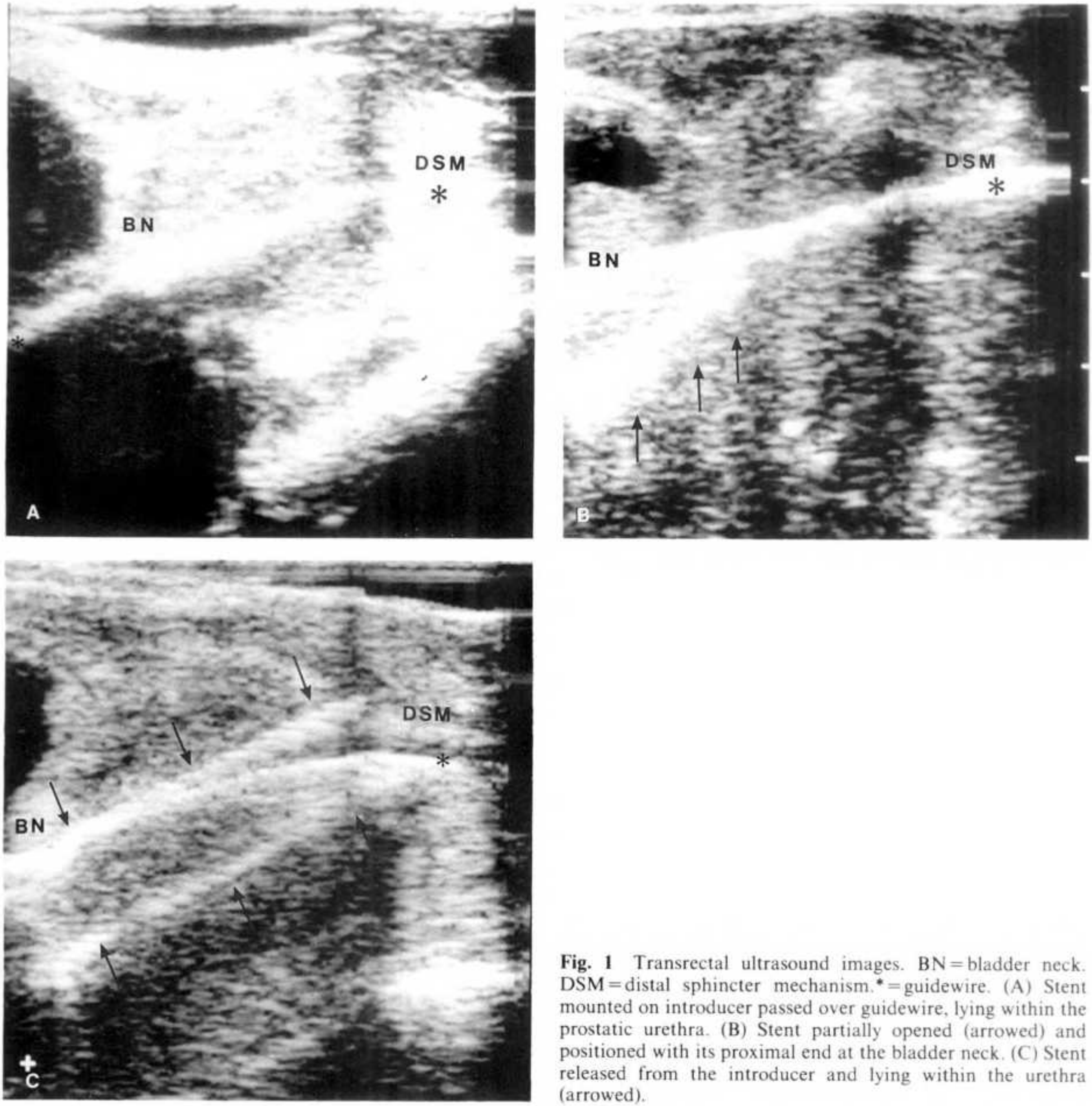

Fig. 1 Transrectal ultrasound images. BN = bladder neck. DSM = distal sphincter mechanism. * = guidewire. (A) Stent mounted on introducer passed over guidewire, lying within the prostatic urethra. (B) Stent partially opened (arrowed) and positioned with its proximal end at the bladder neck. (C) Stent released from the introducer and lying within the urethra (arrowed).

accurately, with 2 mm of the device protuding into the bladder.

All 12 patients experienced transient frequency and urgency following the procedure, but this had usually settled by 1 month following treatment. Accurate placement of the stent proximal to the distal sphincter has preserved sphincteric competence in all patients.

A hyperplastic reaction of the urothelium occurs in the interstices of the stent following insertion and is identical to the reaction previously reported in the dog and human urethra (Milroy *et al.*, 1988). Full epithelial cover of the stent in these patients occurred 6 to 8 months after insertion, slightly later than that reported with urethral stents, after which the hyperplastic reaction settled. In 5 patients (Table) the stent was found to be protruding into the bladder on follow-up cystoscopy. In 2 patients, follow-up at 8 months revealed encrustation with fine spicules of calcification on some of the exposed

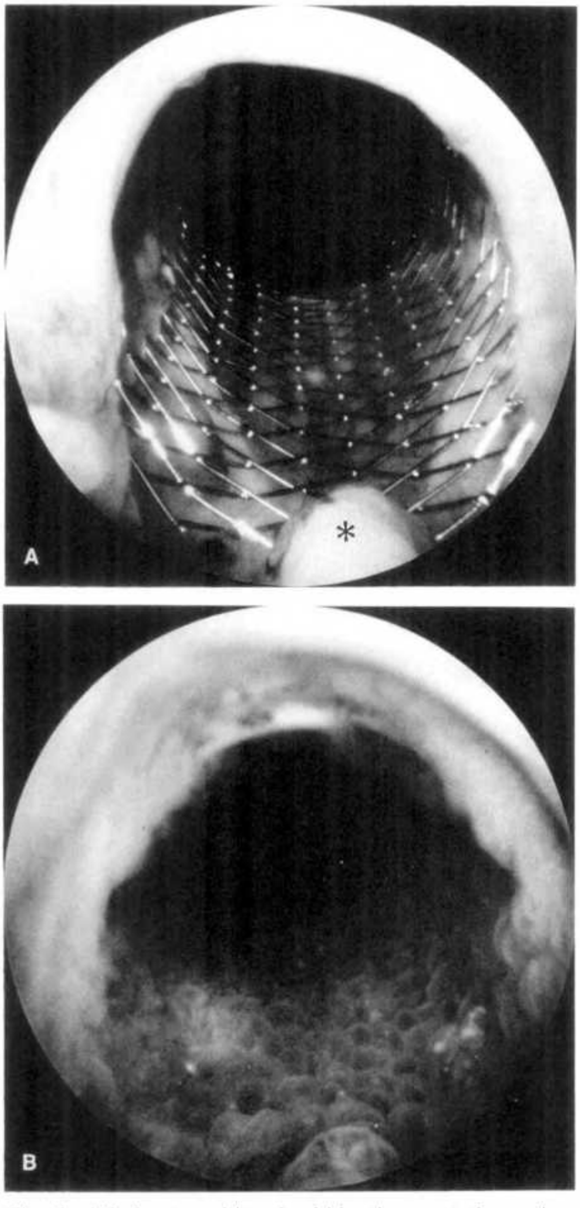

Fig. 2 (A) Stent positioned within the prostatic urethra, demonstrating verumontanum(*) and bladder neck beyond. (B) The same stent as seen in Figure 4A, 6 months after insertion, demonstrating the hyperplastic reaction which subsequently leads to full epithelialisation.

wires. No patient developed infections related to his prosthesis and in no case has subsequent removal of the stent been necessary.

Discussion

This new, permanently implanted urethral stent has now been in use for 2½ years and we have successfully implanted it in more than 50 men with complex urethral strictures. The application of this technique to the prostatic urethra is a logical extension of the procedure but is subject to entirely new limitations and indications. Distal to the prostate the urethra is easily straightened, thin-walled and devoid of any significant intrinsic muscle layer. The prostatic urethral lumen is not straight and in patients with outflow obstruction is rendered even more tortuous by enlargement of the prostate. It must also be remembered that the stromal compartment of the prostate gland possesses a large muscle content under the dynamic control of a rich adrenergic nerve supply. Successful use of the Wallstent in arteries, which also contain a powerful adrenergically innervated smooth muscle component within their walls, produces an interesting parallel (Rousseau *et al.*, 1987; Sigwart *et al.*, 1987).

A particular problem with the use of any stent in the prostatic urethra is accurate placement of the device, since encroachment on to the distal urethral sphincter mechanism will result in impaired continence and protrusion through the bladder neck will limit the chances of subsequent successful urothelial cover. Previous reports have documented the use of "intra-urethral spirals" designed for temporary implantation (Parker *et al.*, 1989). These are, however, subject to all of the disadvantages of an intra-urethral foreign body, including migration, encrustation and infection; in addition, they do not allow subsequent catheterisation or endoscopy of the bladder whilst *in situ*. The procedure reported here is similar in magnitude to that used for a temporary stent but provides a permanent treatment and is not subject to problems of migration or infection. Encrustation at the proximal end of the stent occurred in 2 patients in this study, highlighting the importance of accurate placement. The calcification was easily removed at urethroscopy and since the length of uncovered stent so affected was small and associated with urothelial hyperplasia, it is to be hoped that it will subsequently epithelialise. Migration of the Wallstent is prevented by the radial force exerted by the stent on the walls of the prostatic urethra after it opens. This alone proved adequate to allow satisfactory opening of the stent in 7 cases. In a further 5 cases, balloon dilatation was carried out to a diameter of 12 mm. At subsequent follow-up the calibre of the stent has been maintained in all cases at approximately 35 F, which is more than adequate for the passage of an endoscope.

A major criticism which could be levelled at the

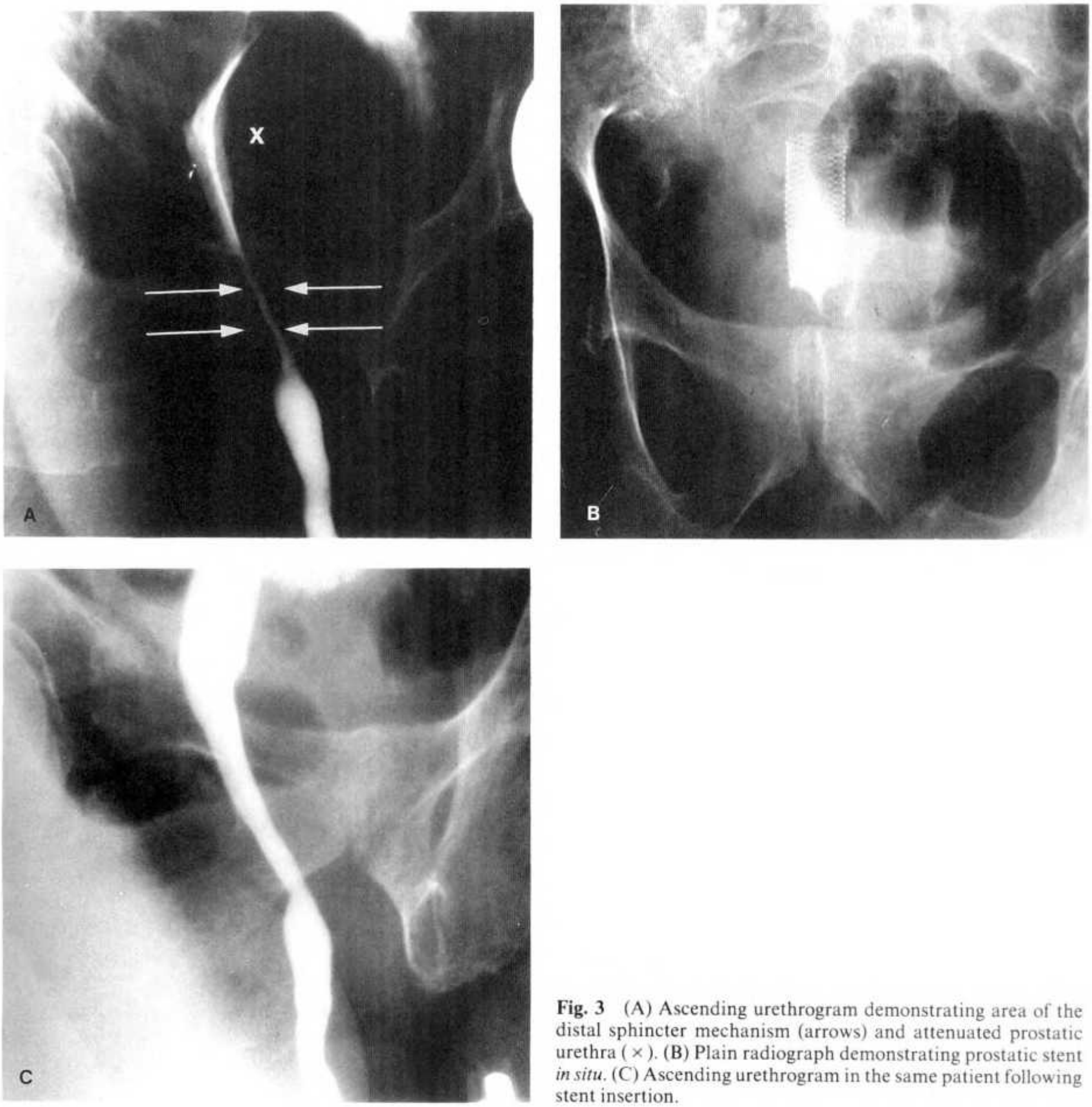

Fig. 3 (A) Ascending urethrogram demonstrating area of the distal sphincter mechanism (arrows) and attenuated prostatic urethra (×). (B) Plain radiograph demonstrating prostatic stent *in situ*. (C) Ascending urethrogram in the same patient following stent insertion.

use of this "permanently" implanted stent is that since it is being inserted under local anaesthesia in patients unfit for general anaesthesia, how can it be removed? Our recent experience with 3 patients has demonstrated that these stents are easily extracted within the first 4 to 6 weeks after insertion if traction is applied to the distal end of the stent; subsequent friction exerted by the walls of the urethra narrows stent calibre and facilitates the procedure. This raises the possibility of inserting these stents on a temporary basis in patients where, despite full urodynamic investigation, the outcome of transurethral prostatectomy remains unknown (Chapple and Milroy, 1989). For example, we have inserted a prostatic stent into 2 patients with Parkinson's disease where there was a mixed picture of detrusor sphincter dyssynergia and prostatic outflow obstruction. Having stented the prostatic urethra, if the patient is improved, the stent can either be left *in situ* or removed at the time of definitive prostatectomy; if the principal abnormality appears to be dyssynergia, the stent can also be removed. A further indication for this technique could be in patients with advanced carcinoma of the prostate, where the stent would provide a simple yet effective relief of outflow obstruction. We believe that endoscopic confirmation of stent positioning is essential; even then, in 7/12 patients in this study the stent was found to protrude through the bladder neck at subsequent review.

In view of the importance of accurate stent positioning, both in urethral strictures and the prostate, we have developed an applicator which allows insertion under full endoscopic control (Fig. 4A). This device uses a standard 0° telescope which can be moved to and fro within the introducer sheath and which has lateral slots which allow the urethra to be visualised (Figs 4B and C). The sheath is pulled back to release the partially opened stent mounted within it. This new technique allows the stent to be almost fully opened and then closed repeatedly until the operator is satisfied with its final position; full deployment occurs only after a safety catch is released.

This study has suggested that the permanently implanted prostatic urethral stent has a useful therapeutic role, providing a safe and effective treatment in patients who are medically unfit for

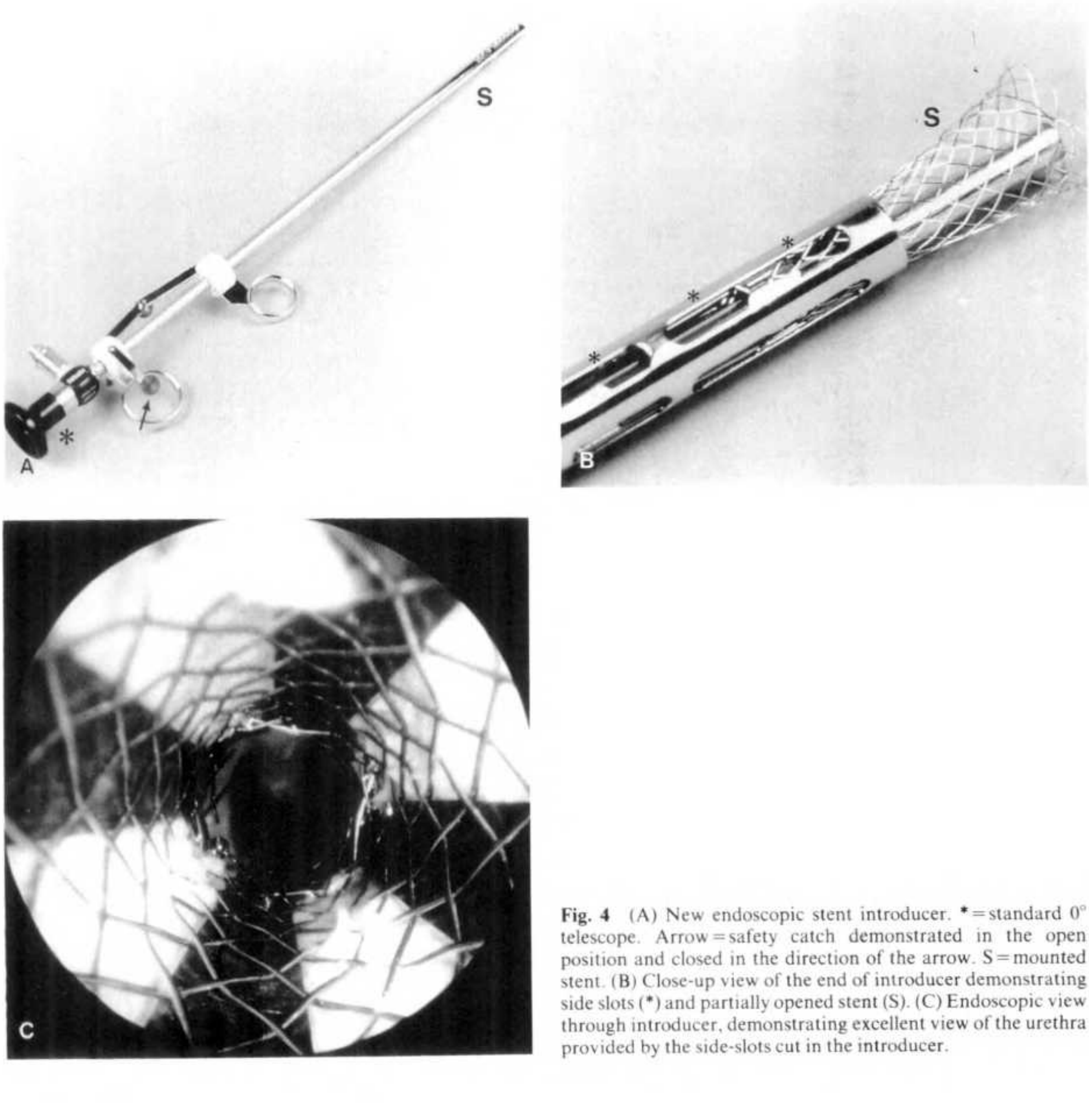

Fig. 4 (A) New endoscopic stent introducer. * = standard 0° telescope. Arrow = safety catch demonstrated in the open position and closed in the direction of the arrow. S = mounted stent. (B) Close-up view of the end of introducer demonstrating side slots (*) and partially opened stent (S). (C) Endoscopic view through introducer, demonstrating excellent view of the urethra provided by the side-slots cut in the introducer.

prostatectomy and with concurrent malignant disease that implies a short life expectancy. We have now treated 33 patients with this technique, with similar results; only the first 12 are reported here because of the short follow-up available for the remainder. At present it is inappropriate to consider this therapy as an alternative to conventional surgery. Further longer-term follow-up of these stents in the urethra is necessary to allow a more complete study of possible complications and failures.

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The Authors

C. R. Chapple, BSc, FRCS, Senior Urological Registrar.
E. J. G. Milroy, FRCS, Consultant Urological Surgeon
D. Rickards, FRCR, Consultant Radiologist

Requests for reprints to· E. J. G. Milroy, Department of Urology, Middlesex Hospital, Mortimer Street, London W1N 8AA.

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The Use of Prostatic Stents in Patients with Urinary Retention who are Unfit for Surgery

An Interim Report

J. McLOUGHLIN, R. JAGER, P. D. ABEL, A. EL DIN, A. ADAM and GORDON WILLIAMS

Departments of Surgery and Radiology, Royal Postgraduate Medical School, Hammersmith Hospital, London; Medinvent, Lausanne, Switzerland

Summary—Under local anaesthesia, 19 patients (18 with acute and 1 with chronic urinary retention) underwent insertion of an expandable stainless steel tubular "stent" into their prostatic urethra under fluoroscopic control. All were considered to be at major risk from prostatic surgery. The 18 patients with acute retention voided spontaneously following the initial stent procedure, but the patient with chronic retention required a period of suprapubic catheterisation. Following the endoscopic insertion of an additional stent this patient also voided spontaneously.

During a follow-up period of 3 to 7 months (mean 4), 4 patients were lost to follow-up. The remaining 15 patients all void spontaneously. Recurrent asymptomatic urinary tract infections were seen in all but 1 patient initially, but none of those who were followed up for over 5 months had evidence of infection.

Although the follow-up period is limited, the results to date demonstrate that the insertion of an expandable prostatic stent is a safe and reliable method of treating acute urinary retention in patients unfit for surgery. Further follow-up is required to assess long-term safety and to exclude late complications.

Transurethral resection of the prostate (TURP) is the current optimal therapy for the relief of bladder outflow obstruction. The associated mortality has declined progressively over the last 3 decades (Mebust, 1988) but patients undergoing prostatic surgery for acute retention still show a higher than expected mortality rate (Malone *et al.*, 1988) and an unchanged morbidity rate (Mebust, 1988). The successful use of a self-expanding, tubular stainless steel stent in the treatment of difficult urethral strictures has been described recently by Milroy *et al.* (1988, 1989). We have described the use of this stent in the treatment of patients with bladder outflow obstruction who were considered unfit for surgery and who had been treated by indwelling urethral catheters for varying periods (Williams *et al.*, 1989). These devices have "pores" which allow epithelialisation to occur and so minimise the long-term risks of displacement and encrustation. These were problems with the original intraprostatic spiral (Fabricius *et al.*, 1983; Flier and Seppelt, 1987) as first described by Fabian (1980). We present our experience with the use of such stents for the relief of bladder outflow obstruction secondary to prostatic obstruction.

Patients and Methods

Nineteen patients aged between 65 and 90 years (mean 75) with permanent indwelling urethral catheters were studied. The duration of catheterisation prior to the study ranged from 1 week to 3 years (mean 15 weeks); 18 patients were catheterised for acute retention and 1 for chronic retention. They were recruited from a number of hospitals throughout the south-east of England. Sixteen patients were assessed by consultant surgeons

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outside the Hammersmith Hospital. Seventeen were considered unfit for prostatectomy because of coexisting medical conditions such as severe cardiopulmonary disease, advanced malignancy or a combination of risk factors placing them at a high risk from prostatectomy: 9 had 1 major risk factor, 4 had 2 and 4 had 3 or more major risk factors, excluding age. Two patients (1 elderly and 1 diabetic) had refused surgery but requested an alternative to an indwelling urethral catheter. Six patients had poor mobility and 3 had moderate mobility. The prostate was benign in 17 and malignant in 2 patients.

Of the 19 patients, 17 had infected urine prior to stenting; 5 had symptoms of bladder instability and 1 had occasional urge incontinence prior to catheterisation.

All patients gave informed consent to take part in the study and were treated on an in-patient basis. A premedication of temazepam (Wyeth Laboratories) 10 mg orally together with cefuroxime (Glaxo Laboratories) 750 mg i.v. was administered 30 min before insertion of the stent.

The procedure was carried out in the radiology department. A preliminary retrograde urethrogram was performed to locate the position of the external sphincter, this being marked with an external skin marker. Using 2% Xylocaine jelly as topical anaesthesia, a 6 F angiographic catheter was used to catheterise the bladder and, under fluoroscopic control, the catheter was replaced over a guide wire with the delivery device (Fig. 1). Withdrawal of the outer sheath of the delivery device allowed the stent to expand along the entire length of the bladder neck and prostatic fossa whilst preserving the integrity of the distal intrinsic sphincter mechanism. Throughout the procedure the guide wire remained in position. Following the procedure the patient received 2 further doses of intravenous antibiotics at 8 and 16 h.

In the initial 9 patients, a 14 F Foley catheter was introduced over the guide wire into the bladder at the end of the procedure. The catheter remained in place for the first 24 h. In the last 10 patients no catheter was inserted.

The following day a retrograde urethrogram was performed (Fig. 2A) to check the position of the stent and the bladder was then filled via the urethrogram catheter (in those patients with catheters inserted at the time of the procedure this was then removed). The patient was invited to void (Fig. 2B).

Flow rates and mid-stream urine specimens were assessed at the end of the first week and at monthly intervals thereafter; 2 weeks after stenting a transabdominal ultrasound estimate of residual urine was made (Fig. 3). In 6 patients an additional transrectal ultrasound scan was also used to visualise the stent (Fig. 4). A 16 F flexible cystoscope (Olympus) was used to visualise the prostatic urethra of 2 patients at 2 months, an additional 2 patients at 3 months (Fig. 5) and a further patient at 4 months.

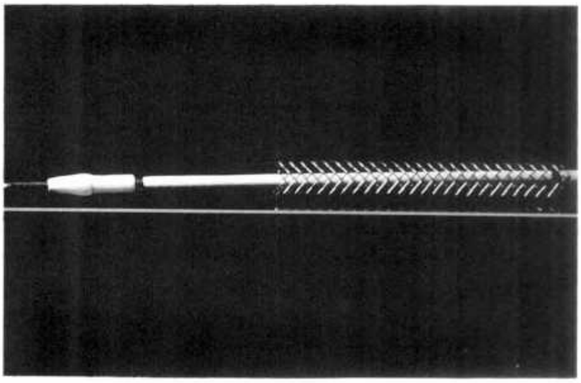

Fig. 1 The delivery device.

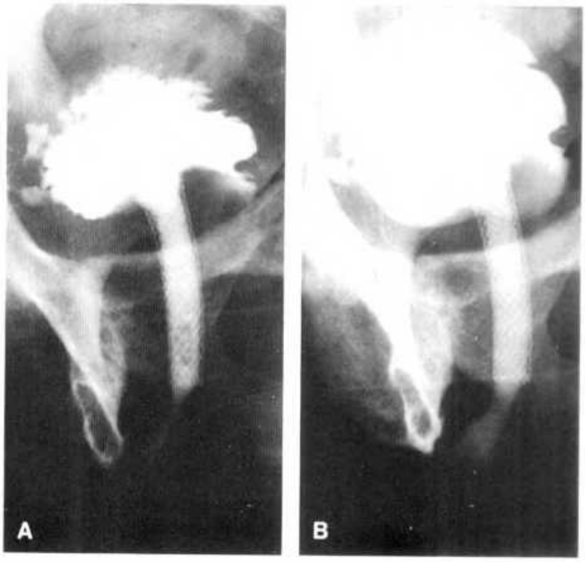

Fig. 2 Retrograde urethrogram showing (A) the position of the stent and external sphincter and (B) the patient voiding.

Results

Following insertion of the stent, 18 of the 19 patients voided spontaneously. The patient who

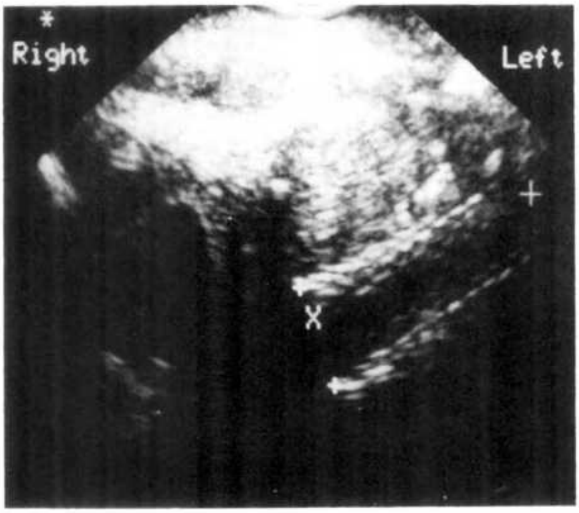

Fig. 3 Transrectal ultrasound showing the prostatic stent lying across the prostatic fossa (+ − + = length of stent).

failed to do so was the only one with chronic retention and he required suprapubic catheterisation for 2 months after the initial procedure. At this stage he underwent suprapubic cystometry which demonstrated a return of detrusor tone. Flexible cystoscopy revealed residual prostatic tissue overlapping the distal extremity of the stent. An additional stent was inserted and he then voided spontaneously.

Following insertion of the stent, the patients' flow rates were measured at the end of the first week and at monthly intervals thereafter. The maximum flow rate at the last time of follow-up for each patient is shown in Figure 6.

Ultrasound assessment of residual urine after stenting demonstrated complete bladder emptying in 17 of the 18 patients who were voiding spontaneously but 1 patient had a residual volume of 300 ml at the end of the first week. Repeat ultrasound examination 1 week later revealed no significant residual volume.

Fifteen patients experienced extreme urgency of urination for the first 3 to 4 days after stenting and in 3 patients this persisted for up to 8 weeks. Eight patients had initial urge incontinence lasting from 3 to 21 days (median 14). Of 6 patients who received Oxybutynin (Tillots Laboratories) for control of their incontinence or urgency. 5 were still taking this on follow-up 8 to 12 weeks after the procedure but only 1 remains symptomatic; 4 of those who had urge incontinence have impaired mobility.

Four patients had demonstrable stress incontinence. In 3 of these this settled spontaneously after 5, 6 and 14 days respectively but in 1 case it persisted despite radiological confirmation of the stent being in a satisfactory position proximal to a clearly defined sphincter.

One patient has minor dribbling requiring the use of a continence pad and this has persisted 3 months after stenting. Ultrasound examination

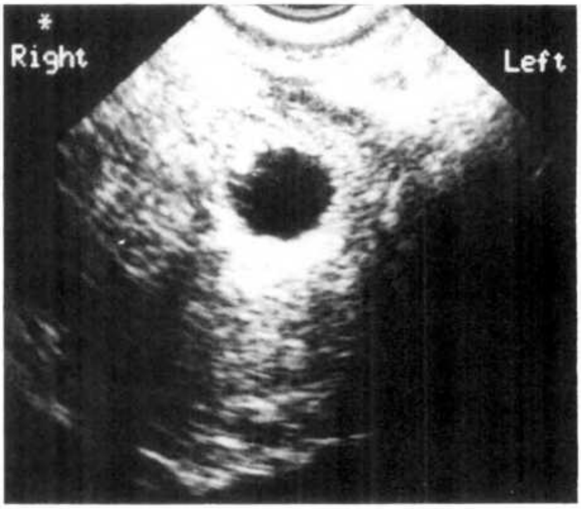

Fig. 4 Transrectal ultrasound showing the diameter of the stent *in situ*. Stent seen in transverse position.

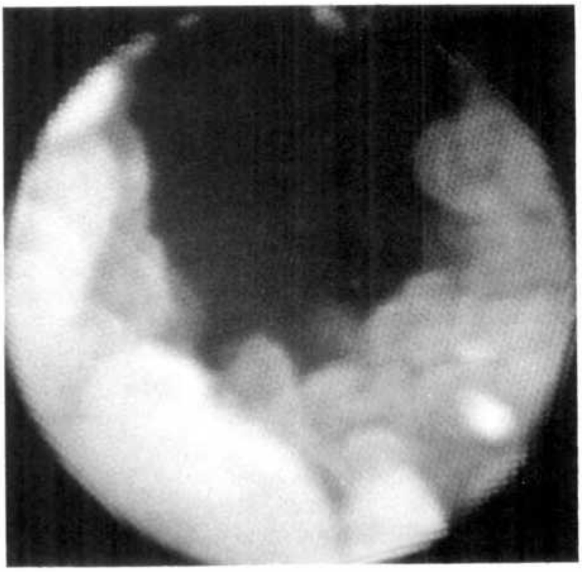

Fig. 5 Appearance of stent after 3 months observed with a flexible cystoscope.

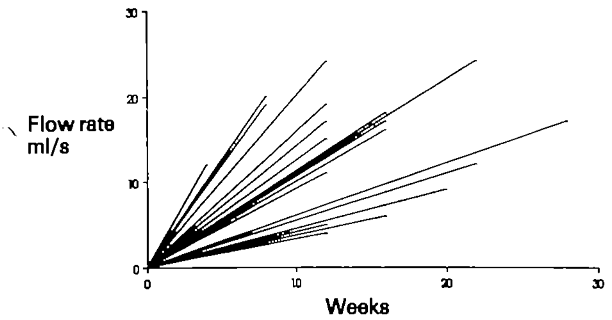

Fig. 6 Peak urinary flow rates at last follow-up.

revealed complete bladder emptying and a retrograde urethrogram demonstrated preservation of the sphincter mechanism.

Initial nocturnal enuresis was noted in 3 patients, either alone or in combination with urge incontinence, and this persisted for 4, 6 and 8 weeks respectively. One patient developed nocturnal enuresis at 8 weeks following exacerbation of his Parkinson's disease. Retrograde urethrography demonstrated a tight stricture in his penile urethra. Following optical urethrotomy and better control of his Parkinson's disease, this enuresis resolved.

Two patients found the procedure painful, and required post-operative opiate analgesia; 4 experienced penile pain (persisting for 24 h in 3 cases and for 3 weeks in 1).

Despite prophylactic antibiotics, 1 patient developed septicaemia 4 days after stenting but this responded to intravenous antibiotics.

Seventeen patients had infected urine when the stent was inserted. All but 1 had recurrent asymptomatic urinary infections at some stage in the initial 4 months but none of the patients followed up for 5 months or more has evidence of infection. Only 2 were symptomatic throughout this period, 1 with epididymo-orchitis and 1 with dysuria. Three patients were treated with antibiotics by their family practitioners, the urine of 2 of these remaining infected. With the exception of the patient with epididymo-orchitis and the patient who developed septicaemia, no patient received antibiotics during the follow-up period.

Endoscopic inspection revealed a florid hyperplastic appearance of the urothelium at 2 months (Fig. 5) which became less pronounced at 4 months. Epithelialisation of the stent was well established at 4 months.

During the follow-up period 3 patients died of unrelated causes at 8, 12 and 20 weeks respectively and 1 was lost to follow-up following admission to another hospital.

Discussion

This study is the first to detail the medium-term results obtained in 19 patients with a permanent indwelling urethral catheter who were unfit for surgery and who were treated by insertion of a stainless steel expandable tubular prostatic stent. All 18 patients with acute retention voided spontaneously with no residual urine on follow-up. The only patient who did not void spontaneously had chronic urinary retention and following a further stent insertion he too voided.

The wide distribution of flow rates in these patients initially, and on subsequent follow-up, is in part a reflection of the inability of a number of patients to retain enough urine to give a voided volume of 250 ml or more. Ultrasound examination confirmed that these patients were emptying their bladders completely. The high initial incidence of urgency and urge incontinence was not restricted to patients with poor mobility but presented more of a problem in this group. This may be due to stretching of the bladder neck by the stent or persistent bladder instability following resolution of outflow obstruction. It appears that the longer these patients are followed up the less of a problem the incontinence becomes, with only 2 patients (1 marked and 1 minimal) having problems at 3 months.

We chose not to treat the post-operative urinary infections as it was hoped that they would clear once complete epithelialisation of the prosthesis occurred, either spontaneously or following a course of appropriate antibiotics.

Epithelialisation of the stents has been shown to be partial at 6 months and complete at 12 months when placed in the penile urethra of dogs and examined microscopically (Milroy *et al.*, 1988). Our results show that on visual inspection, epithelialisation in the prostatic urethra is well established at 3 months. It is by this process of epithelialisation that our stent can be distinguished from the "urological spiral" (Fabian, 1980). In these earlier attempts to relieve urinary retention the spiral was inserted under cystoscopic control. Unlike the stent, however, the device did not epithelialise and this led to troublesome encrustation and displacement (Fabricius *et al.*, 1983; Flier *et al.*, 1987) with replacement or removal being required in a number of patients. Our initial results suggest that a higher proportion of patients show a favourable result following insertion of stents compared with intraprostatic spirals (Fabian, 1984; Flier and Seppelt, 1987).

Once epithelialised, the stent is unlikely to be displaced by urethral catheterisation but prior to that time the use of suprapubic catheterisation is necessary to avoid displacement of the stent into the bladder. For this reason the use of these stents in patients with atonic bladders who may require prolonged catheterisation should be carefully considered. This stent has to be considered a permanent alternative to prostatectomy, unlike the urological spiral and Prostakath (which may be removed easily by grasping cystoscopically), and thus is unsuitable for "trials" in patients with equivocal obstruction or in those who require an alternative to catheterisation prior to a definitive operation (Parker *et al.*, 1989).

In this initial study we inserted the stents under radiological control, which we believe allows satisfactory visualisation of the bladder neck and urethral sphincter mechanism, and we have noted only transient stress incontinence in a minority of patients. We are, however, evaluating the efficacy of endoscopic visualisation of the bladder neck and sphincter mechanism when inserting the stent.

In this high risk group of patients we observed no mortality related to the procedure and the morbidity rate was comparable to that of transurethral resection of the prostate. These stents, on initial follow-up, represent an alternative to indwelling urinary catheters in this particular group of patients, but a prolonged period of follow-up is required before they can be considered in fitter patients.

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The Authors

J. McLoughlin, FRCS, Urological Registrar, Hammersmith Hospital

R. Jager, MD, Radiology Registrar, Hammersmith Hospital.

P. D. Abel, ChM, FRCS, Senior Lecturer/Honorary Consultant in Urology, Hammersmith Hospital.

A El Din, MD, Medinvent.

A Adam, FRCR, Consultant Radiologist, Hammersmith Hospital.

Gordon Williams, MS, FRCS, Consultant Urologist, Hammersmith Hospital.

Requests for reprints to Gordon Williams, Department of Surgery, Hammersmith Hospital, Du Cane Road, London W12 0HS.

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Osmotic and Metabolic Sequelae of Volumetric Overload in Relation to the TUR Syndrome

A. N. GHANEM and J. P. WARD

Department of Urology, District General Hospital, Eastbourne

Summary—In an attempt to understand the pathophysiology of the transurethral resection syndrome this prospective metabolic study was conducted on 100 consecutive patients undergoing transurethral resection of the prostate (TURP). The volume of glycine absorbed, intravenous fluid given and blood loss were calculated, and serum osmolality, sodium and glycine were measured before, during and after operation. The mean volume of glycine absorbed, fluid gain and blood loss were 0.6, 1.57 and 0.356 litres respectively. The mean weight of prostate resected was 30.8 g and resection time was 56.5 min. The mean serum osmolality dropped from 291 to 286 mOsm/l, sodium dropped from 138 to 132 mmol/l and glycine concentration increased from 293 to 3599 μmol/l post-operatively.

Ten patients developed signs suggestive of the TURP syndrome. Multiple regression analysis showed that the most consistent statistically significant factors in relation to the syndrome were volumetric gain and hypo-osmolality. The latter proved to be the only significant factor later post-operatively. The increase in serum glycine and drop in serum sodium concentrations were the best serological markers, reaching significance only after excluding volumetric gain and osmolality from the analysis.

The TURP syndrome was first described by Creevy (1947) as acute water intoxication causing haemolysis, jaundice and acute tubular necrosis. Osmotic solutions such as glycine, mannitol and cytal were then introduced but a complex clinical syndrome continued to occur (Hagstrom, 1955). Hyponatraemic shock induced by glycine absorption was described by Harrison *et al.* (1956), who introduced 5% sodium chloride for treatment.

Several authors have measured the volume of glycine absorption (Casthely *et al.*, 1983), changes in serum sodium and electrolytes (Sellevold *et al.*, 1983), sodium loss in urine (Whisenand and Moses, 1961) as well as changes in blood volume, haemoglobin (Hb) and red cell mass (Colapinto *et al.*, 1973). The syndrome is well described in retrospective studies and individual case reports as a bizarre clinical picture which may affect some patients following TURP. The patient may present with coma and paralysis, respiratory distress or arrest, renal failure and cardiac dysrhythmia or arrest and these may occur in any combination.

Circulatory shock affecting patients with the TURP syndrome has frequently been described but has usually been attributed to blood loss (Logie *et al.*, 1980), cardiogenic or septicaemic shock (Bertrand *et al.*, 1981; Bird *et al.*, 1982). Erroneous diagnosis may lead to inappropriate treatment with further blood and fluid infusions (Norris *et al.*, 1973), which may cause death due to brain, myocardial and lung necrosis (Lessels *et al.*, 1982). The discrepancy between the results of prospective trials and the bizarre presentation of the syndrome has given rise to doubts as to its existence and to the theory of ammonia intoxication (Hoekstra *et al.*, 1983). However, dilutional hyponatraemia, with an incidence of 7% and 1% mortality, does occur (Rhymer, 1985) and a relationship with excessive fluid absorption is now accepted (Rao, 1987). The results of a 5-year investigation, which aimed at

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quantifying volumetric gain and its osmotic sequelae in relation to the TURP syndrome (Ghanem, 1988), are now reported.

Patients and Methods

A prospective study of 100 patients undergoing TURP was carried out with approval of the Medical Ethical Committee. A standard procedure was performed, using an irrigating resectoscope (Storz), 1.5% glycine irrigant (at a height of 80 cm above the heart) and suction drainage (Haemonetics Cell Saver IV), which measured blood loss. The absorbed volume of 1.5% glycine was the difference between the volume used and returned. Bumetanide 1 mg was given at the end of the procedure. The volume and type of per- and 24-h post-operative intravenous fluids infused were recorded. Pre- and post-operative urinary cultures were performed on all patients and blood cultures were done on those showing signs of post-operative circulatory shock.

Blood electrolytes, serum osmolality, glycine, alanine and serine aminoacids were measured on admission to hospital, after anaesthetic induction, on termination of the procedure and on the first post-operative morning. Further measurements were carried out on symptomatic patients, who were randomised between hypertonic sodium chloride and conservative treatment.

The osmolality of fluids used in this study were: 1.5% glycine 196, Hartmann's 257, normal saline 287 and 5% dextrose 297 mOsm/kg.

Statistical analysis

Data were analysed statistically using a computer (Macintosh SE, Apple Computers Ltd) with a commercially available database and statistical packages (Stat View 512+, Brain Power Inc). Patients served as their own controls by a comparison of their pre- and post-operative findings. Data are presented as the mean and standard deviation (SD). Student's t test, multiple regression analysis and χ^2 tests were used for comparative statistical analysis.

Results

The mean age of the patients was 74 years (SD ± 4), weight was 70.8 kg (±8.6), weight of resected prostatic tissue was 30.8 g (±21.7) and resection time was 56.5 min (±27.3). The mean volume of 1.5% glycine used for irrigation per procedure was 16.73 litres (±10.38). The mean per-operative volume of glycine absorbed, total fluids gained and blood loss were 0.6 (±0.7), 1.57 (±0.98) and 0.356 (±0.148) litres respectively. The mean 24-h fluid intake and urine output from the start of surgery were 3.25 (±1.557) and 4.85 (±2.37) litres respectively.

Ninety-three per cent of patients had a blood loss <0.4 litres; 7% had a blood loss ranging from 0.45 to 1.3 litres. Five patients were re-transfused with autologous blood recovered from the glycine effluent. Only 1 of the 15 patients who received a blood transfusion had fulfilled the criteria of the TURP syndrome and received 1 unit of blood: he was thought to have suffered hypovolaemic shock, although the data indicated volume overload (*vide infra*).

Volume of 1.5% glycine absorbed

Figure 1 shows a histogram of the volume of glycine absorbed. Nine patients had a negative balance due to blood and urine loss; 59 patients absorbed 0–1 litre, 20 absorbed 1–1.5 and 12 absorbed >1.5 litres. The surgeon's observations on breaching the prostatic capsule and opening the venous sinuses were significantly related to the volume of glycine absorbed and the development of the TURP syndrome ($P = 0.0001$). These observations were recorded in 11 patients who absorbed >1 litre of glycine, of whom 7 developed the TURP syndrome and 4 did not. A further 3 patients developed the syndrome (*vide infra*) and in these cases neither perforation of the capsule nor opening of the venous sinuses was observed by the surgeon. The subjective assessment of bleeding, however, was overestimated by a factor of 3–10 times the measured volume of blood loss.

Neither the weight of the resected prostate, resection time nor blood loss reached statistical

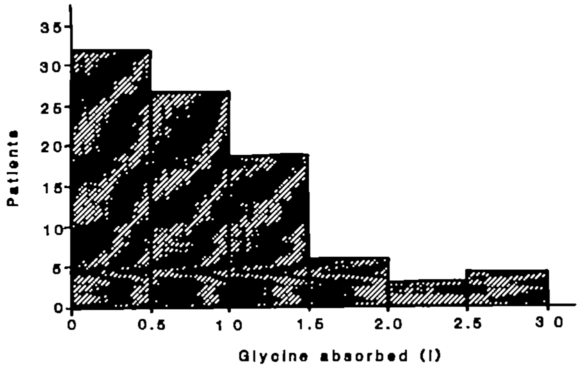

Fig. 1 Frequency distribution of patients according to the volume of 1.5% glycine absorbed. Nine patients who had a negative balance, due to blood and urine loss, are excluded

significance in relation to the volume of glycine absorbed and development of the TURP syndrome.

Volumetric gain and hyponatraemia

A total of 20, 10 and 4% of all patients showed a drop in post-operative serum sodium concentration of >10, >15 and >20 mmol/l respectively. Figure 2 shows a significant relationship between the volume of glycine absorbed and the post-operative changes in serum glycine and sodium concentrations ($P=0.0001$). A significant relationship between the post-operative drop in serum sodium concentration and total volumetric gain, including IVI fluids, was also observed ($P=0.0001$).

Serum chemical and haematological changes

Serum osmolality, chemical and haematological values at the pre-determined times are shown in Table 1. All patients had normal serum osmolality and sodium levels on admission; 3 were hyponatraemic in hospital before surgery, 1 from diuretics, another from steroid therapy and the third had prostatic carcinoma with metastases.

Post-anaesthetic induction changes

Comparison of the serum osmolality and solute concentrations after anaesthesia and before the start of surgery with normal values on admission (B v A, using paired *t* test) showed a decrease in serum proteins, albumin, calcium, CO_2, Hb, packed cell volume (PCV) and measured osmolality ($t=0.0001$). Serum sodium and white cell count (WCC) also decreased ($t<0.05$). Multiple regression analysis revealed that the patient's age and histology of prostatic tissue showed a significant relationship with the drop in serum proteins ($P<0.05$). The type of anaesthesia was related to the drop in CO_2. The patient's weight was related to the drop in serum sodium levels.

Post-surgical changes

Comparison of the post-surgical with the post-anaesthetic induction values (C v B) revealed a significant drop in serum osmolality, sodium, calcium, proteins, albumin, alkaline phosphatase, Hb and PCV. Serum glycine, glucose and potassium increased. These changes were significant in both symptomatic and asymptomatic patients ($t=0.0001$). The drop in serum osmolality was significant in symptomatic cases only ($t=0.006$). Table 2 compares the means of symptomatic and asymptomatic patients.

The volume of 1.5% glycine absorbed, the type and the volume of intravenously infused fluids were significant in relation to the drop in serum osmolality, sodium and proteins concentration ($P<0.001$). The abnormal rise in serum glucose, reaching a level of 11.2 (SD ± 5.7) mmol/l, was related to the per-operative 5% dextrose infusion, and the rise in serum glycine concentration was related to the per-operative volume of the glycine irrigant absorbed ($P=0.0001$).

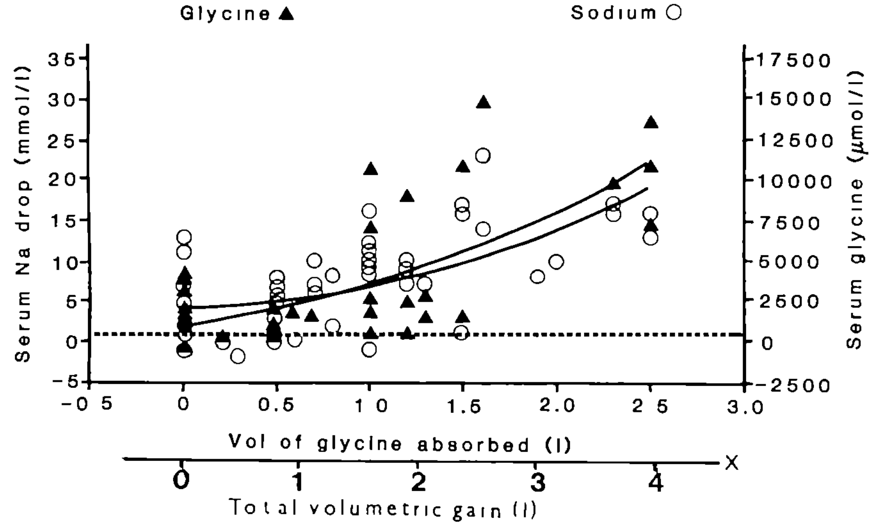

Fig. 2 Scatter graph of the 100 patients with curve fits shows relationship of the volume of 1.5% glycine absorbed to the post-operative serum glycine [▲], [▲$Y=3675X+658\ 6$, $R=0\ 73$, $P=0.0001$], and drop in serum sodium concentration [○], [○$Y=4.7X+3.6$, $R=0.7$, $P=0.0001$] The bottom horizontal axis [X′] represents the total volume of fluids gained during the operation—[○$Y=3.3X'+0.9$, $R=0.67$, $P=0.0001$]. The dotted line represents the normal level of serum glycine concentration (<300 µmol/l).

Table 1 Mean Osmolality, Chemical, Haematological Values and Glycine Aminoacids

Time	*A*	*B*	*C*	*D*
Osm measured	291	288	286	**281**
Osm calculated	290	288	**281**	**283**
Osm gap	1	0.3	**5**	−1
Sodium	138	137	**132**	**134**
Potassium	4.4	4 5	**4.7**	**4.2**
Urea	7.1	7 0	7.0	7.9*
Glucose	6.5	6.2	**11.2**	**8.0**
Protein	65	62	**55**	**58**
Albumin	40	38	**34**	**35**
Calcium	2.27	2.16	**2.04**	**2.11**
Co2	28	26	26	27
Bilirubin	9	9	9	**12**
AST	19	18	18	20
Alk Phosphatase	100	100	91*	**90**
Hb	13.8	13.4	**12.4**	**12.5**
PCV	0.408	0.39	**0.364**	**0.369**
WCC	9.3	8.6	8.6	**11.6**
Glycine (μ mol/l)	—	293	**3599**	290
Serine	—	155.6	255*	157 5
Alanine	—	335	539*	456.9*

The values shown in **bold** at the immediate (C) and 24-hour (D) post-operative times are highly significant compared with the pre-operative (B) values ($P = 0.0001$, using paired t test)
* $P < 0$ 05

Compensatory 24-h post-operative changes

Comparison of the serum changes 24-h post-operatively with the immediate post-surgical values (D v C) showed a continuing decrease in serum osmolality ($t = 0.0001$). Serum sodium, proteins, albumin, calcium, Hb, PCV and alkaline phosphatase increased spontaneously, although remaining low, while serum glycine and glucose concentrations decreased ($t = 0.0001$). All returned to normal (Table 1). Serum urea, bilirubin, AST and WCC were significantly raised ($t < 0.05$).

Table 2 Immediate Post-operative Means of Data comparing Symptomatic and Asymptomatic Patients

	Symptomatic	*Asymptomatic*
No. of cases	10	90
Glycine absorbed (l)	**1.94**	0.45
Total fluid gain (l)	**3.5**	1.36
Blood loss (l)	0.321	0.36
Increase in serum glycine concentration (μmol/l)	**10499.00**	**1508.00**
Serum sodium drop	**17.7**	**4.6**
Serum osmolality drop	**11.4**	0.7

Bold figures are significant ($P < 0.05$). Note that changes in serum sodium and glycine are significant in both symptomatic and asymptomatic cases, while significant change in serum osmolality characterises symptomatic cases only

Statistics and symptomatic patients

The above means and standard deviations (Table 1) and paired t tests were insensitive in revealing symptomatic patients with TURP syndrome. Based on pre-defined biochemical and clinical criteria for the syndrome, the results obtained were analysed. A patient who had a drop in serum sodium concentration >15 mmol/l, who absorbed more than 1.5 litres of glycine and suffered hypotension, bradycardia or dysrhythmia on ECG tracing with any of the following clinical signs: restlessness, confusion, muscle twitches, circulatory shock, coma, paralysis and respiratory distress, was considered to be suffering from the TURP syndrome. Eight patients fulfilled both the biochemical and clinical criteria while 88 patients did not. Two patients, despite having a drop in serum sodium of 16 mmol/l, remained clinically asymptomatic, while another 2 patients who showed signs of the syndrome had a drop in serum sodium concentration of only 14 and 13 mmol/l.

The TURP syndrome

Hypotension associated with bradycardia was a consistent feature of the syndrome and affected 10 patients; initial hypertension occurred in 2 cases only. Episodes of bradycardia on ECG tracing and hypotension occurring during the operation and recovery period were taken from the anaesthetic records and affected 16 patients; 10 had the TURP syndrome with a mean total per-operative volumetric fluid gain of 3.54 litres (SD ± 0.6). The other 6 patients who had either bradycardia (4) or hypotension (2) in isolation had a mean volumetric gain of 3 litres (±0.5). The remaining 84 patients had a mean total gain of 1.24 litres (±0.6).

Restlessness, confusion and muscle twitches affected all patients; 7 showed signs of circulatory shock with hypotension, coldness, pallor, peripheral shut-down and oliguria. Respiratory wheezes and crepitations affected 5 of the symptomatic patients. None suffered cardiac or respiratory arrest and there were no deaths despite a drop in serum sodium concentration of >20 to a level below 120 mmol/l in 4 patients, each of whom gained >3.5 litres (Fig. 2).

The mean post-operative serum sodium concentration of the 10 clinically symptomatic patients was 120.7 mmol/l (±3). The mean drop in serum sodium was 17.4 mmol/l (±4.4) and osmolality was 11.4 mOsm/kg (±8.4). The mean volume of glycine absorbed, total fluids gained and blood loss were 1.94, 3.54 and 0.32 litres respectively (Table 2).

Multiple regression analysis revealed that a volumetric fluid gain of 3.54 litres (±0.6) was the most consistent statistically significant factor in relation to the clinical signs ($P=0.0007$). The drop in serum osmolality was also significant ($P=0.02$), but the changes in serum glycine, sodium, albumin, Hb and calcium did not reach statistical significance (Table 3). Serum glycine and sodium changes were significant ($P=0.003$ and 0.01) when volumetric overload and hypo-osmolality were excluded from the analysis. A volumetric gain of 3.5 litres (±0.6) and a drop in serum osmolality of 11.4 mOsm/kg characterised patients with the TURP syndrome (Table 2).

Treatment

Five of the 10 patients who showed signs of the TURP syndrome were treated with 5% sodium chloride infused at a rate of 200 ml/20 min. The other 5 patients, plus the 2 patients with an asymptomatic drop in serum sodium of 16 mmol/l, were treated conservatively. In the conservatively treated group, 3 patients were given atropine for bradycardia, aminophylline for respiratory distress and a further dose of diuretic (bumetanide 1 mg). Two patients appeared to suffer hypovolaemic shock despite volumetric overload and they had all the criteria of the TURP syndrome, they were treated by "guarded" volume expansion. The first patient received 1 unit of blood and 1 litre of Haemaccel with bumetanide (2 mg), atropine and aminophylline; the second patient received 1.5 litres of Haemaccel, atropine and a further dose of bumetanide). The 2 patients with asymptomatic hyponatraemia were each given a further dose of diuretic.

Response to treatment

Figure 3 shows the changes in serum sodium and osmolality of patients treated with hypertonic sodium and those treated conservatively. Those treated with hypertonic sodium responded promptly and recovered fully, passing between 2.5 and 4.5 litres of urine. Serum sodium concentration was elevated by the end of the infusion to 132.5 mmol/l (±0.2) and had returned to normal levels by the next morning. No complications or residual signs were observed in this group.

In the conservatively treated group, 2 patients had spontaneously recovered clinically by the next morning and biochemically after 48 h. The 2 patients treated with "guarded" volume expansion; they responded to the diuretic and each passed 3.5 litres within 4 h of treatment. One of these patients had cerebral symptoms of lethargy and confusion for 48 h after surgery, as did another 3 of the conservatively treated patients. The second patient treated with volume expansion was comatose and had left-sided hemiplagia, thought to be a cerebrovascular accident, on the morning after surgery. He remained fluid overloaded as his urine output was followed by further intravenous fluid infusions. He recovered after a delayed infusion of 5% NaCl. Comparing the results of the 2 types of treatment, using the χ^2 test, showed a statistically significant difference ($P=0.01$).

Delayed cerebral signs

Seven patients, 4 from the conservatively treated group and 3 who had asymptomatic post-operative hyponatraemia with a drop in serum sodium of >10 and <15 mmol/l, were lethargic and confused 21 h (±2.5) after surgery and remained so for up to

Table 3 Multiple Regression Analysis of Total Per-operative Fluid Gain, Drop in Measured Serum Osmolality (OsmM), Sodium, Albumin, Hb and Increase in Serum Glycine occurring immediately Post-operatively in Relation to Signs of the TURP Syndrome. (Volumetric gain and hypo-osmolality are the only significant factors)

Multiple Regression Y_1 Postop signs 6X variables

Beta Coefficient Table

Parameter	*Value*	*Std Err*	*Std. Value*	*t Value*	*P*
INTERCEPT	0.773				
Fluid Gain (L)	0.847	0.228	1.044	3.721	0.0007
OsmM (C−B)	0.033	0.014	−0.375	2.42	0.0212
Na+ (C−B)	0.095	0.049	0.616	1.95	0.0597
Alb (C−B)	0.062	0.087	0.239	0.713	0.4809
Hb (C−B)	−0.282	0.246	−0.368	1.149	0.2587
Glycine (C−B)	−4.973E−5	5.975E−5	−0.242	0.832	0.4112

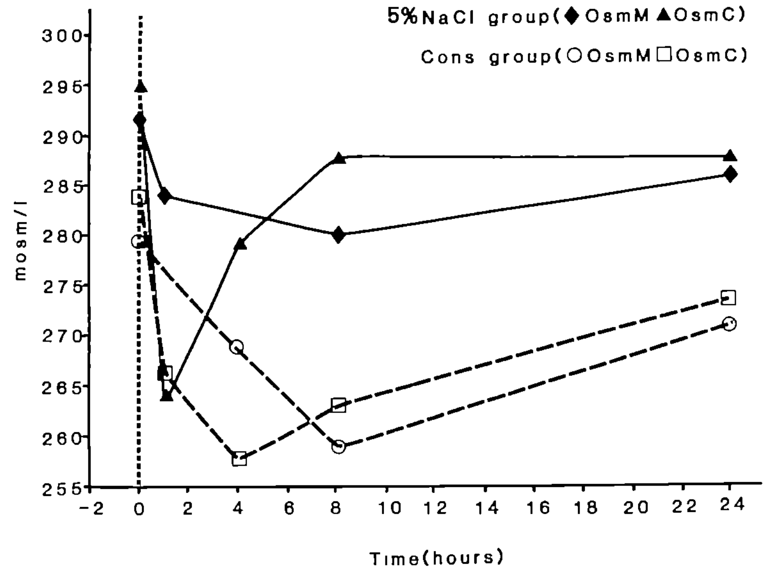

Fig. 3 Mean changes in measured serum osmolality (OsmM) and calculated osmolality (OsmC) in patients with the TURP syndrome, comparing those infused with 5% hypertonic sodium (solid lines) and those treated conservatively (slashed lines). OsmC was calculated from the formula 2 × Na+urea+glucose in mmol/l of serum concentrations (Worthley *et al.*, 1987), thus reflecting changes in serum sodium concentrations. The vertical dotted line represents the start of the operation (Time B), followed by C, C1, C2 (end of treatment) and D respectively.

48 h. One patient became comatose and hemiplegic on the first post-operative morning. Serum osmolality of the 7 confused patients was 267; in the patient with coma and paralysis it was 250 and in the remaining 92 asymptomatic patients it was 283 mOsm/l. Hypo-osmolality was the only significant factor in relation to delayed cerebral signs ($P = 0.0001$).

Discussion

The results of this study have shown that the TURP syndrome is precipitated by sodium-free fluid volumetric overload, the result of glycine absorption and intravenously infused fluids. The measured mean volumes of glycine absorption, blood loss and changes in serum electrolytes are similar to those reported by Sellevold *et al.* (1983) and Rhymer *et al.* (1985). The data indicate that a volume of more than 2 litres, gained in 1 h, can lead to the TURP syndrome; >3.5 litres precipitates shock and multiple system dysfunction (Fig. 2). No patient with the syndrome had a blood loss exceeding 0.4 litres (Table 2); unlike hypovolaemic and septicaemic shock, 5% NaCl was shown to be the treatment of choice as further isotonic fluid and blood infusions were contraindicated.

The immediate mean post-operative changes in serum solutes and osmolality (Table 1) were glycine (+1128%), glucose (+72.3%), alkaline phosphatase (−30%), proteins and albumin (−15%), calcium, Hb and PCV (−10%), potassium (+4.5%), sodium (−4.35%) and osmolality (−1.7%). Our study showed that these changes were proportionally and significantly related to the volume and type of fluid gained. However, most of these changes have previously given rise to individually recognised syndromes and to a hypothesis explaining the TURP syndrome.

Hyponatraemia (Arieff, 1986; Ayus *et al.*, 1987), hyponatraemic hypoalbuminaemic syndrome (Dandonna *et al.*, 1985), hypocalcaemia (Rhymer *et al.*, 1985; Malone *et al.*, 1986), water intoxication and the glucose-petressin syndrome known in obstetrics are examples of syndromes induced by sodium-free fluid volumetric overload which have been attributed to the apparent changes in serum solute concentrations. Also, the rise in serum concentration of solutes gained from the absorbed fluid such as glucose, glycine and sorbitol (Allen *et al.*, 1981; Norlen *et al.*, 1986) or metabolites presumed to originate from them such as ammonia (Hoekstra *et al.*, 1983) and oxalates (Malone *et al.*, 1986) have been incriminated as a possible pathogenesis for the TURP syndrome. In the present series, however, neither hypoalbuminaemia, hyponatraemia, hypocalcaemia nor hyperkalaemia was significant in relation to the pathogenesis of the syndrome.

The results of this study showed that the mean drop in serum osmolality was significant in symptomatic cases, but not overall (Berg *et al.*, 1962; Sellevold *et al.*, 1983; Norlen *et al.*, 1986). The changes in serum sodium and glycine were significant in both symptomatic and asymptomatic cases (Table 2).

The immediate post-operative serum osmolality gap, occurring despite the increase in serum glucose, was filled by serum glycine, which does not enter the formula for calculated osmolality (Worthley and Thomas, 1987). The half-life of glycine has been reported to be as short as 85 min (Norlen *et al.*, 1986). This study showed that serum glycine returned spontaneously to normal levels within 24 h and none of the therapeutic measures employed in this study was directly involved in glycine metabolism or clearance.

While the serum chemical and haematological changes were spontaneously returning to normal during the 24-h post-operative period by endogenous homeostatic correction, serum osmolality continued to fall. Hypo-osmolality proved to be the only significant factor in causing the delayed signs of the TURP syndrome. These findings suggest that hypo-osmotic injury to the brain and other cells of vital and non-vital organs occurs, and when of sufficient degree causes hypo-osmotic shock (Ghanem, 1988). Desmond (1970) observed the relationship between marked hypo-osmolality and the severe cerebral and pulmonary complications of the TURP syndrome. Wright and Gann (1962) proved that induced severe hyponatraemia, without hypo-osmolality, remains asymptomatic.

Osmotic and volume receptors are the main regulators of volumetric overload. Osmotic receptors regulate body water and sodium concentration and protect cells against excessive changes, thus serving to keep body osmolality constant. Volumetric overload, however, causes bradycardia and rarely produces hypertension. The increase in arterial and central venous pressure is transient (Sellevold *et al.*, 1983) and affected 2% of our patients. Hypotension and bradycardia were more consistent signs of volumetric overload. These observations were reported by Logie *et al.* (1980) but they thought bradycardia was inappropriate and the hypotension was attributed to hypovolaemia and blood loss.

The mechanism by which volume overload induces hypotension and shock is not clear. It may be related to a disturbance of the dynamics of capillary circulation which causes heart failure among other system failures. It has been suggested that hypo-albuminaemia lowers the oncotic pressure and so disturbs Starling's forces across the capillary membrane, leading to loss of intravascular fluid and causing interstitial oedema (Guyton and Coleman, 1968). This has also been suggested as an explanation of the circulatory shock seen in the TURP syndrome (Desmond, 1970; Sellevold, 1983).

Judging by the post-operative dilution in haemoglobin, PCV, proteins and albumin (mainly intravascular contents), symptomatic patients were in a state of hypervolaemia not only after surgery but also up to 24 h post-operatively. They were therefore in a state of hypervolaemia yet also hypotensive and shocked. This was the most confusing aspect of the pathogenesis of the TURP syndrome in particular and syndromes related to volumetric overload in general.

The paradoxical finding that volumetric overload affected intravascular pressure, impairing tissue perfusion and causing shock in which hypoalbuminaemia was insignificant, suggested inconsistency with the hypothesis for capillary-interstitial fluid exchange proposed by Starling (1896). The fact that the capillary is encircled at the inlet by the precapillary sphincter inspired the suggestion that it may induce a Venturi effect. Further studies have revealed the totally different roles of the arterial and venous pressures in regulating a simulated capillary-interstitial fluid transfer (Ghanem, 1988). In the light of these new findings, future studies are justified in order to explore the effects of volumetric excess on vascular pressures and tissue perfusion, as this may prove relevant to the pathogenesis of multiple organ failure.

The TURP syndrome may be prevented by avoiding fluid absorption and excessive intravenous fluid infusion. Glycine absorption may be minimised by avoiding breaching the prostatic capsule and opening venous sinuses—leaving a rim of tissue lining the capsule. When venous sinuses are opened, rapid arrest of bleeding by diathermy, catheter tamponade or even termination of the procedure are reasonable steps. Serum glycine and sodium estimations are useful markers for early detection of excessive glycine absorption. Avoiding further volumetric overload, inducing diuresis and correcting hyponatraemia and hypo-osmolality by hypertonic sodium infusion are effective in treating the TURP syndrome. Perhaps a rapid test of serum glycine concentration (Glycine-stix) may prove to be of use in the operating theatre.

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The Authors

A. N. Ghanem, FRCSE, MD(Urol), Consultant Urological Surgeon, Egypt.

J. P. Ward, MS, FRCS, Consultant Urological Surgeon, District General Hospital, Eastbourne.

Requests for reprints to A N. Ghanem, P O Box 213, Mansoura 35511, Egypt.

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Fluid and Electrolyte Dynamics during Development of the TURP Syndrome

R. G. HAHN

Department of Anaesthesiology, Huddinge University Hospital, Huddinge, Sweden

Summary—Signs and symptoms, circulatory changes and the diffusion of fluid and electrolytes were examined over 10-min periods in the course of 12 transurethral resections of the prostate (TURP) during which more than 1 litre of glycine solution was absorbed. Signs of the TURP syndrome were seen in 10 patients. During the first 20 min of absorption there was hypervolaemia, a marked diffusion of electrolytes from the interstitial space to the plasma, and elevation of central venous pressure. Patients who developed hypertension (n = 6) and chest pains (n = 3) had a smaller blood loss than those who did not. After 20 min of irrigant absorption there was an increased flow of fluid from the plasma to the interstitial space coupled with only a small diffusion of sodium. This promoted hypovolaemia and hypotension.

It is widely known that absorption of irrigating fluid during transurethral resection of the prostate can produce a potentially life-threatening syndrome, including disturbance of haemodynamics and mental function (Norris *et al.*, 1973; Osborn *et al.*, 1980). According to prospective studies, absorption of irrigant occurs during most TURPs, but the "TURP syndrome" is observed in only 2 to 7% of all resections (Rhymer *et al.*, 1985; Mebust *et al.*, 1989).

The aim of this investigation was to study the patients' pathophysiology during development of the TURP syndrome by comparing circulatory changes and other symptoms with the calculated diffusion of fluid and electrolytes to and from the bloodstream. The patients were selected from a series of 200 TURPs performed during the last 5 years at this hospital. In all cases, careful measurement of fluid balance and relevant blood samples was made at 10-min intervals during the course of resection (Hahn *et al.*, 1988).

Patients and Methods

The study group included 12 men aged from 59 to 79 years with benign hypertrophy of the prostate gland who had undergone transurethral resection (operation time 52 ± 13 min (mean ± SD)). The criterion for selection was absorption of more than 1 litre of irrigating fluid during surgery that resulted in immediate hyponatraemia, indicating that the absorption was intravascular (Hahn *et al.*, 1988).

Procedure

Consent for the study was obtained in all cases. Mild premedication was given orally. During induction of epidural anaesthesia and in the course of surgery the patients were given 1.5 to 2.0 litres of Ringer's acetate solution (containing 130 mmol sodium and 4 mmol potassium/l). When loss of blood was excessive, 500 ml dextran 70 in normal saline (Macrodex, Pharmacia, Sweden) were also administered. No erythrocytes were transfused during surgery. A Storz 27 F resectoscope and the intermittent bladder-filling technique were used. Isotonic glycine solution, with (n = 6) or without (n = 6) 1% ethanol as a tracer of absorption, was used as irrigating fluid during the procedure. After operation the irrigant was 0.9% saline.

Measurements

Blood samples. At the end of each 10-min period throughout the resection, blood was collected for determination of haemoglobin concentration (Hb),

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haematocrit (B-EVF), serum sodium (S-Na) and serum potassium (S-K) concentrations. Analysis was performed by standard methods (Hahn *et al.*, 1988).

Volumetric fluid balance. The volume of irrigant absorbed was measured volumetrically every 10 min throughout the procedure. The following method was used: the irrigating fluid bags were weighed before and after use. The irrigating fluid bag and the collecting bucket were changed every 10 min and fluid volumes and blood loss were carefully measured. The volumetric fluid balance obtained in this way was corrected for the mean of the Hb concentration recorded at the beginning and at the end of the 10-min period (Hahn, 1987a).

Circulatory monitoring. Heart rate and arterial pressure were recorded every 5 min. In 6 patients the central venous pressure (CVP) was measured continuously on an HP 78342 A (Hewlett-Packard, Göblingen, W. Germany). Data on the CVP measurements in 2 of these patients have been presented previously (Hahn *et al.*, 1988).

Calculations

Blood volume. Variations in the volume of blood and plasma were estimated indirectly by the haemoglobin dilution method (Hahn, 1987b); this involves calculation of the patient's pre-operative total haemoglobin content, from which losses are subtracted. The Hb concentration is used as an indicator of dilution. Possible errors inherent in the calculations appear to be small (Hahn, 1989a). The method yields similar results to those obtained by the ^{131}I-RISA technique (Hahn, 1987b).

Diffusion of water and electrolytes. The plasma content of electrolytes was calculated as the product of plasma volume and electrolyte concentration. The diffusion of water and electrolytes between the plasma and the interstitial fluid in each patient was computed from the changes in plasma volume and electrolyte content over each 10-min period with a correction made for blood loss, irrigant absorption, and the water and electrolytes provided by the intravenous fluid supplementation.

Statistics. The methods of statistical analysis were simple linear regression and the paired and unpaired Student's *t* tests.

Results

Table 1 shows the total volume of irrigant absorbed and electrolyte changes during the operations, the pattern of absorption, the blood loss and symptoms of the TURP syndrome. The absorption over 10-min periods and the results of the calculations of blood volume and the diffusion of fluid, sodium and potassium are presented in Figure 1. In Figure 2 the total blood volume, plasma volume, sodium and potassium concentrations in the circulation are expressed as a percentage of the values obtained immediately before absorption of the irrigant.

The volume of Ringer's acetate solution given intravenously during 10 min of irrigant absorption was 95 ± 45 ml (mean ± SD).

Bleeding was greater during irrigant absorption than during periods of no absorption in the same patient ($n = 6$; means 193 and 71 ml, SD 130 and 27 respectively; $P = 0.04$).

Blood volume and ion diffusion

Blood volume (Fig. 1, upper). During 0 to 10 min of absorption there was a significant increase in blood volume (0.27 ± 0.18 l; $P < 0.001$); between 10 and 20 min this remained unchanged; between 20 and 30 min of absorption the blood volume decreased in 9/10 patients by 0.28 ± 0.24 l (mean ± SD; $P < 0.01$). However, 1 patient who absorbed 680 ml showed a further increase in blood volume. Between 30 and 40 min of absorption it was unchanged in the 2 patients who recorded the largest absorption over this period, and decreased in the remaining patients.

Diffusion of sodium. Between 0 and 20 min of absorption there was a net flow of sodium ions from the interstitial space to the plasma (Fig. 1, middle). Hence, although the absorption produced immediate hyponatraemia, there was an increase in the total plasma content of sodium ions (Fig. 2). The quotient of the flow of sodium by the "ideal flow" (defined as the flow required to maintain an unchanged serum level) showed that $70 \pm 18\%$ (mean ± SD) of the dilution effect on serum sodium by the absorbed irrigating fluid was corrected immediately. However, with massive absorption (> 800 ml/10 min), this dropped to 30 to 50%.

Diffusion of potassium (Fig. 1, lower). Potassium ions readily entered the plasma to counteract the dilution caused by the potassium-free irrigant, and in this way maintained the serum concentration. However, during all 10-min periods, relatively more

Table 1 Operative Data and Signs and Symptoms in 12 Patients

Patient no.	Age (years)	Volume of irrigant absorbed (ml)	Pattern of absorption	Electrolyte changes (mmol/l) S-Na	Electrolyte changes (mmol/l) S-K	Blood loss (ml)	Chest pains	Hyper-tension	Hypotension During TURP	Hypotension After TURP	Nausea and vomiting
1	79	1090	End of TURP	−10	0.0	768					
2	70	1100	Middle and end	−6	+0.1	178	×	×		×	
3	78	1130	Continuous	−8	+0.8	898		×			
4	69	1375	End of TURP	−8	+0.3	400		×			
5	65	1906	Continuous	−6	+0.7	1256					×
6	59	1910	End of TURP	−12	+1.1	580	×	×		×	×
7	76	2261	Continuous	−8	+0.4	476	×	×	×		
8	76	2488	Continuous	−7	0.0	553					
9	71	2610	End of TURP	−9	+2.0	1425			×	×	
10	77	2810	Continuous	−16	+0.5	609				×	×
11	76	2813	Continuous	−13	+0.6	689		×			
12	67	4330	Middle and end	−22	−0.4	740			×	×	×

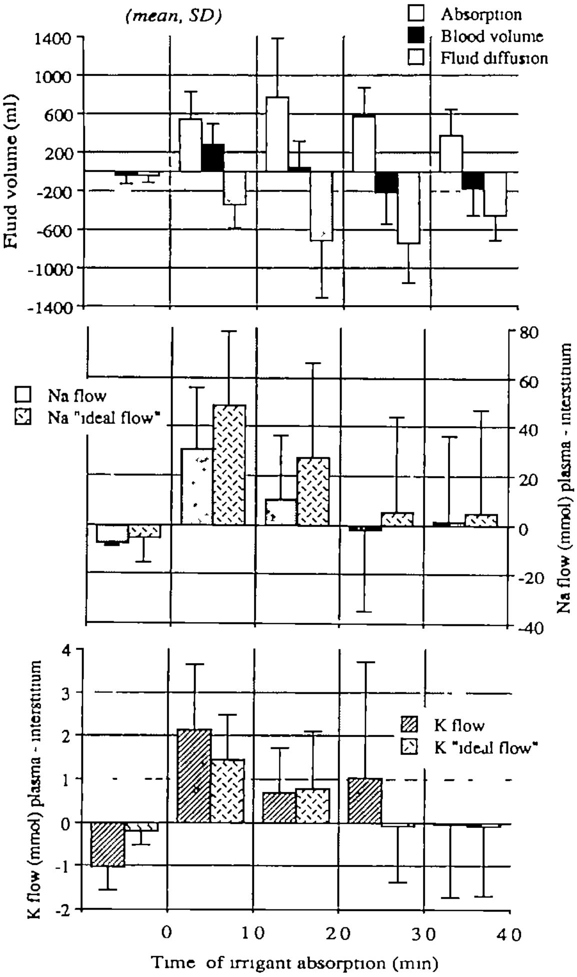

Fig. 1 Volume of irrigant absorbed, change in blood volume, and diffusion of fluid (*upper*), sodium (*middle*) and potassium (*lower*) into (+) and out from (−) the plasma compartment in 12 patients.

potassium entered the plasma in association with the absorption of 500 to 800 ml/10 min, resulting in an increase in the S-K concentration.

Circulatory changes

Hypertension. In 6 patients there was a rise in systolic arterial pressure by >10 mmHg after 20 min of absorption ($P<0.007$; paired t test) (Table 2) which correlated with the change in blood volume during 0 to 20 min of absorption (Fig. 3).

Heart rate. In 5 patients the heart rate decreased by 5 to 15 beats/min during absorption of the irrigant; it was unchanged in 6 patients and increased in 1.

Central venous pressure (CVP). The relationship between the change in CVP and the volume of irrigant absorbed during any 10-min period is shown in Figure 4. Increasing absorption resulted in elevation of the CVP, but it fell sharply as soon as there was a reduction in the absorption rate.

Hypotension during surgery. In 3 patients there was a sudden decrease in systolic arterial pressure to 80 mmHg or lower at 30 to 35 min of ongoing absorption (Table 1) and this coincided with marked reductions in the rate of irrigant absorption. Rapid haemoconcentration preceded the onset of hypotension; the patients recorded a decrease in blood volume by 0.3, 0.8 and 0.25 l during the 10-min period before arterial pressure dropped. In 2 of these 3 patients the blood volume was lower at this point than before induction of epidural anaesthesia.

Hypotension after surgery. Five patients suddenly became hypotensive at the end of the operation or within 1 h thereafter. Blood volume could not be

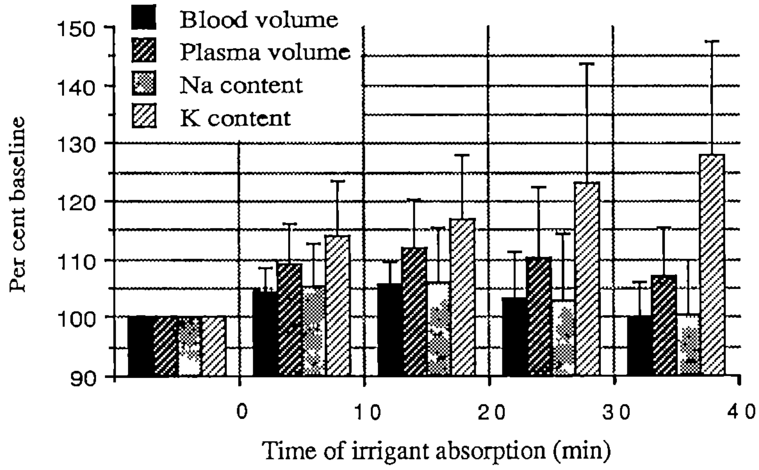

Fig. 2 Changes in blood and plasma volume and the total plasma content of sodium (Na) and potassium (K) during irrigant absorption.

estimated after surgery in patients 9 and 12 because erythrocytes were being transfused, but only in patient 10 was data collected for calculation of the blood volume immediately before the onset of hypotension. This showed a value 0.48 l below the pre-operative estimation.

Symptoms

Initial symptoms. A prickling or burning sensation in the hands or neck (n = 4) always occurred during the first 10 min of absorption, in connection with rather high absorption rates (630 ± 130 ml; mean ± SD). Patient 12 reported nausea when large absorption began (absorption rate 640 ml/10 min) and patient 4 complained of respiratory distress (absorption rate 750 ml/10 min). Patient 10, who had a history of 2 myocardial infarctions, became cyanotic when 1,565 ml/30 min had been absorbed. Marked skin pallor was noted in patients 10 and 12 in connection with rapid massive absorption.

Chest pains (n = 3) (Table 1) occurred just after hypertension had developed, 20, 25 and 30 min respectively after the onset of irrigant absorption. In 2 of these patients the chest pains were preceded by depression of the ST-T segment on the ECG. There was no difference between the absorption rate in these patients and in those who did not report chest pains, but they recorded less bleeding (108 ± 43 ml and 231 ± 156 ml during 10 min respectively; mean ± SD; $P < 0.04$).

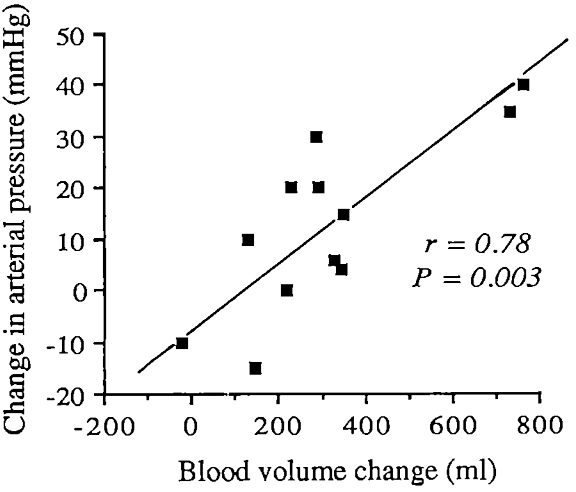

Fig. 3 Change in arterial systolic blood pressure *versus* blood volume change during the first 20 min of irrigant absorption.

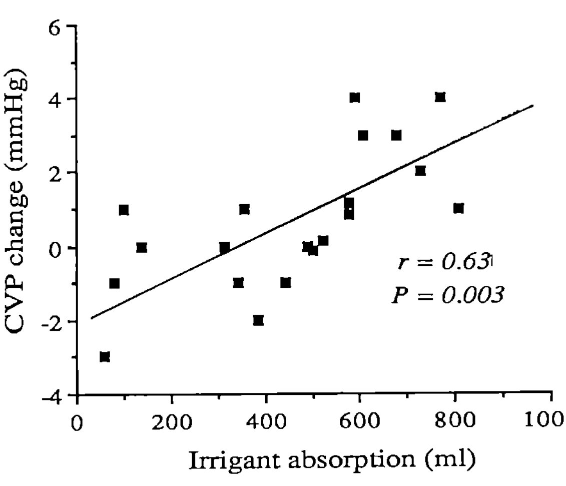

Fig. 4 Change in central venous pressure (CVP) *versus* irrigant absorption during 10-min periods of irrigant absorption.

Post-operative symptoms consisted of nausea, vomiting and slight confusion (n=4) (Table 1). These symptoms developed about 1 h after the operation was completed and persisted for 1 to 3 h.

Patients 1 and 8 did not develop any symptoms.

Discussion

The measurements carried out at 10-min intervals, together with assessment of fluid and electrolyte dynamics, offer a uniform picture of the pathophysiologial events associated with absorption of electrolyte-free glycine solution during TURP. Two phases with different features can be distinguished. The first involves the build-up of hypervolaemia, a marked diffusion of sodium and potassium ions from the interstitial fluid into the circulation, and elevation of central venous pressure. After about 20 min of ongoing absorption, hypertension may develop. However, as absorption continues an increasing amount of water diffuses from the plasma to the interstitial fluid. During the second phase there is a sudden decrease in blood volume, CVP and arterial pressure. Various degrees of hyperkalaemia usually develop. When large volumes of irrigating fluid are absorbed (>500 ml/10 min), the onset of this second phase can be delayed, but it usually occurs after 30 to 35 min of ongoing absorption.

Thus for some time after the start of absorption the bloodstream acts as a barrier that limits the impact of irrigant absorption on the interstitial fluid and on the cells. During the second phase, however, there is a marked escape of fluid from the plasma to the interstitial fluid coupled with only a small exchange of sodium between these compartments (Fig. 1, upper and middle). The "barrier" effect of the bloodstream then breaks down and further absorption of irrigant directly enters the interstitial compartment.

Various symptoms of the TURP syndrome can occur in susceptible individuals at different stages during this course of events. In the present study, the serum sodium deficit at the end of surgery was often as small as 6 to 9 mmol/l, but most patients still experienced mild forms of the syndrome (Table 1).

A rise in arterial pressure is known to be a circulatory response reflecting pick-up of irrigating fluid (Harrison *et al.*, 1956), although it does not always occur (Norris *et al.*, 1973; Osborn *et al.*, 1980). Three hypotheses have been advanced to explain why hypertension develops in some patients but not in others. These maintain that the critical factor for the development of elevated arterial pressure is the hypervolaemia *per se* (Maluf *et al.*, 1956), the patient's cardiac function (Desmond, 1970) or his tendency to react in a certain way to cardiovascular stress (Marx *et al.*, 1960). In the present study, the patients showing an increase in blood volume in connection with irrigant absorption were usually the ones who developed a rise in systolic pressure (Fig. 3), which suggests that the first of the 3 hypotheses is most correct. The hypervolaemia and hypertension, on the other hand, could be attributed to small blood loss rather than large absorption (Table 2).

Chest pains have been reported to be a symptom of the TURP syndrome (Harrison *et al.*, 1956; Norris *et al.*, 1973). In this study they coincided with the onset of hypertension, which suggests that they can probably be explained by increased cardiac oxygen demand resulting from a combined effect of rapid elevation of both pre-load (CVP) and after-load (arterial pressure).

Hypotension is a consequence of irrigant absorption often, but not always, preceded by arterial hypertension. It appears to have major prognostic value, as judged by reports of ensuing renal failure (Conger and Karafin, 1957; Bandhauer and Madersmacher, 1969), cardiovascular collapse and death (Norris *et al.*, 1973; Osborn *et al.*, 1980; Rhymer *et al.*, 1985). The concept of "dilutional hyponatraemic shock" (Harrison *et al.*, 1956), or that hypotension is the result of poor cardiac capacity (Desmond, 1970), has been used to explain this puzzling combination of hyperhydration and low blood pressure.

The present study suggests that the principal pathophysiological event leading to hypotension from absorption of irrigant is the escape of fluid

Table 2 Systolic Arterial Pressure before and during Irrigant Absorption

	Systolic blood pressure (mmHg, mean ± SD)	
Time of absorption (min)	*Hypertensive (n=6)*	*Normotensive (n=6)*
0	118±11	126±26
10	125±9	124±21
20	144±13	126±28
30	134±34 (n=5)	118±36 (n=5)
40	135±21 (n=3)	128±38 (n=3)
Volume of irrigant absorbed (ml)	1778±674	2312±1222 (NS)
Blood loss (ml)	491±254	965±310 (P=0·016)

from the plasma to the interstitial compartment during the second phase of development of the TURP syndrome, which leads to hypovolaemia. At least 5 mechanisms promote this fluid diffusion. They include elevated arterial and/or venous hydrostatic pressure (Table 2, Fig. 4), and low oncotic pressure owing to dilution of blood proteins (Hahn, 1989b). A "rebound effect", similar to the dispersal of plasma after cessation of an intravenous infusion of saline (Moore *et al.*, 1966), is likely to be involved. Two mechanisms promote plasma escape by contracting the extracellular space and causing loss of water and sodium. During ongoing irrigant absorption, irrigant water is normally removed from the extracellular space at the impressive mean rate of 230 ml/10 min (Hahn, 1988, Hahn *et al.*, 1989). Bleeding during irrigant absorption includes an "undetected" sodium loss because some of the plasma sodium at this time is derived from the interstitial fluid (Fig. 1, middle). Finally, the urinary excretion of irrigating fluids seems to result in a marked natriuresis. In experiments with volunteers, almost 50 mmol of sodium were excreted in connection with intravenous infusion of 1 litre of isotonic glycine or mannitol solution (Hahn *et al.*, 1989).

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The Author

R. G. Hahn, MD, PhD, Consultant in Anaesthesiology, Huddinge University Hospital, S-141 86 Huddinge, Sweden.

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Identifiable Factors in Post-prostatectomy Haemorrhage: the Role of Aspirin

C. J. E. WATSON, A. M. DEANE, P. T. DOYLE and K. N. BULLOCK

Department of Urology, Addenbrooke's Hospital, Cambridge

Summary—Post-operative haemorrhagic complications following the ingestion of aspirin have been reported after several types of surgery, most notably coronary artery bypass surgery. In this study, aspirin ingestion also appeared to be a significant aetiological factor in post-prostatectomy haemorrhage. This is explained in terms of its inhibitory effect on platelet aggregation. A history of aspirin ingestion should be carefully sought and its haemorrhagic implications considered prior to prostatectomy.

The introduction of regular monthly audits into this practice identified 16 patients who, under the criteria used for the audit, were considered to have unacceptable haemorrhage following transurethral prostatectomy. These 16 patients were from a total of 205 undergoing prostatectomy in the 8 months of the audit. They were compared with a control group of patients matched for type of anaesthesia, histology, resection weight, age and blood pressure. Pre-operative medications were studied to see if there were any significant differences.

Patients and Methods

The criteria used for identifying patients with unacceptable haemorrhage are detailed in Table 1, the presence of any 1 of the 3 criteria being regarded as significant. The criteria take into account the weight of prostatic resection, an important variable directly related to blood loss. All resections were performed by 1 of 2 consultants or a senior registrar.

Audit of all patients undergoing surgery is performed on a regular basis and complications (such as haemorrhage and chest infection) recorded as an "on-going" process. Monthly meetings are held in the department to review and discuss the data obtained.

Sixteen patients fulfilled the criteria for unacceptable haemorrhage over an 8-month period. They were compared with a control group ($n=32$) selected randomly on statistician's advice from patients undergoing resections over the same time period. Patients with malignant glands were then excluded from this group, leaving 23 patients. The 2 groups were analysed with respect to the patient's age, pre-operative blood pressure, weight of resected gland, surgeon and mode of anaesthesia to see if the populations were matched.

Results

There was no significant difference between the 2 groups with respect to age, systolic blood pressure, resected weight, prostatic histology, surgeon or mode of anaesthesia (Table 2); 31% of the study

Table 1 Audit Criteria for Unacceptable Haemorrhage

	*Blood transfusion requirement**	
	Resected weight (g)	*Transfusion requirement*
A	<15	Any transfusion
	15–40	>2 units
	>40	>4 units
B	Continued bleeding prolonging in-patient stay	
C	Bleeding requiring re-operation	

*Haemorrhage was regarded as unacceptable if blood transfusion was required to maintain the circulating blood volume in the peri- and post-operative periods.

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Table 2 Comparison between Control and Haemorrhagic Groups

	Control (n=23) Mean (SD)	*Bleeding (n=16) Mean (SD)*	*Significance*
Age (years)	71 (6.5)	72 (6.5)	t=0.52 ns
Weight resected (g)	38 (17)	47 (23)	t=1.41 ns
Systolic BP (mmHg)	149 (26)	155 (21)	t=0.75 ns
General anaesthesia (%)	52	64	ns*
Aspirin (%)	0	31	$P<0.01$†

*χ^2 for standard error of percentages.
†Fisher's exact test—see text.

population were taking aspirin pre- and peri-operatively and, although this was not a formal study of the effect of aspirin ingestion on post-prostatectomy haemorrhage, this seemed to be a highly significant difference which was easily explicable on pathological grounds ($P<0.01$ by Fisher's exact test).

Discussion

Blood loss in both the operative and post-operative periods is directly related to the weight of gland resected, with values of 20 to 37 ml/g being reported (Perkins and Miller, 1969; Lewi *et al.*, 1983; Freedman *et al.*, 1985; Wilson *et al.*, 1988). The weight of the gland, as well as the operator's experience, influences the speed of resection and this is also related to blood loss (Wilson *et al.*, 1988).

The presence of urinary infection contributes to post-operative haemorrhage, in particular to secondary haemorrhage. Harvey *et al.* (1986) showed a significant correlation between post-operative infection and secondary haemorrhage but the incidence was not influenced by a course of post-operative co-trimoxazole.

The histology of the resected gland is important, and increased bleeding from benign glands when compared with malignant glands has been reported (Bejjani *et al.*, 1983). Many studies have made no such distinction.

The influence of different types of anaesthesia, *e.g.* regional (spinal or epidural) or general, has been studied but no conclusive difference noted (Freedman *et al.*, 1985). Other possible variables contributing to blood loss are the age of the patient and the blood pressure, bleeding being more severe in older patients with hypertension.

Of drugs contributing to haemorrhage after prostatectomy the most commonly studied is heparin, administered subcutaneously as prophylaxis for venous thrombo-embolism. Conflicting results have been reported (Halverstadt *et al.*, 1977; Kass *et al.*, 1978; Sleight, 1982; Bejjani *et al.*, 1983; Wilson *et al.*, 1988). There have been few studies on the effect of aspirin on post-prostatectomy haemorrhage but its effect after other surgical procedures is well documented.

Following coronary artery bypass surgery, mediastinal blood loss in patients on aspirin increases by up to one-third (Rubin, 1978; Torosian *et al.*, 1978; Livesey *et al.*, 1988). Amrein *et al.* (1981) showed an increase in blood loss after total hip replacement of 400 ml and noted that aspirin increased the bleeding time by a mean 1.6 min compared with the pre-operative level (mean 4.2 min). Post-tonsillectomy haemorrhage has also been shown to occur more commonly in patients given aspirin than in those receiving paracetamol 1 h post-operatively (Carrick, 1984).

Two studies have described the use of aspirin in patients undergoing prostatectomy. Gavriliuk (1987) reported a high incidence of haemorrhagic complications in patients given aspirin prior to open prostatectomy (23/42). Mongin *et al.* (1983) compared the use of aspirin and subcutaneous heparin in the prophylaxis of venous thrombosis. They showed an increased incidence in bleeding (as measured by duration of urethral catheterisation post-operatively and the need for transfusion), but the study group was small and the increase was not statistically significant.

Our observations confirm those made in other branches of surgery, namely that aspirin significantly increases bleeding in the early post-operative period.

Aspirin acts in 2 ways: firstly, it inhibits platelet aggregation by acetylating cyclo-oxygenase, thus inhibiting the production of thromboxane A_2 ($T \times A_2$); secondly, it inhibits the production of prostacyclin (PGI_2) by vascular edothelium. Following a single 300 mg aspirin tablet the inhibition of $T \times A_2$ production lasts for several days (the lifetime of a platelet since it synthesises little or no new protein), while recovery of prostacyclin production occurs within hours (Kennedy, 1984). The former effect contributes to the increased bleeding time and blood loss and is also important in the use of aspirin for prevention of transient ischaemic attacks and myocardial reinfarction. In the wake of the second report of the ISIS group (ISIS-2, 1988) and recent literature regarding aspirin in the treatment of transient ischaemic attacks, it is likely that increasing numbers of patients in the age group presenting for prostatectomy will be taking aspirin regularly.

In the absence of evidence to the contrary, a history of aspirin ingestion should be actively sought and its use discouraged for 10 days pre-operatively; abstinence should be continued until the risk of post-operative bleeding has ceased.

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The Authors

C J. E Watson, FRCS, Honorary Research Registrar
A M. Deane, formerly Senior Registrar Now Consultant Urologist, Ashford.
P. T Doyle, FRCS, Consultant Urologist
K N. Bullock, FRCS, Consultant Urologist

Requests for reprints to: C. J. E Watson, Department of Surgery, Level 9, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ

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Prostatic Cancer with Bone Metastases: Serum Alkaline Phosphatase (SAP) as a Predictor of Response and the Significance of the SAP "Flare"

J. MACKINTOSH, J. SIMES, D. RAGHAVAN and B. PEARSON

Urological Cancer Research Unit, Department of Clinical Oncology and Ludwig Institute for Cancer Research, Royal Prince Alfred Hospital, Sydney, Australia

Summary—The predictive value of serum alkaline phosphatase (SAP) and of prostatic acid phosphatase (PAP) for response to treatment (NPCP criteria) was retrospectively assessed in patients with bone metastases from prostate cancer. Fifty-one patients had SAP measured at the start of treatment and at 1 and 2 months. In 31 of these, corresponding PAP levels were also available at each time point. SAP/PAP profiles at 2 months were classified as "increased" (increment 15% or greater), "decreased" (reduction greater than 15%) or "stable", compared with baseline levels. An additional category, SAP "flare", was also identified (SAP increment greater than 15% at 1 month, with subsequent fall at 2 months).

There was a strong association between the SAP profile at 2 months and the response category, whereas the PAP profile at 2 months was more weakly associated. Using results from the 31 patients with both SAP and PAP profiles, the level of SAP was significantly better in predicting the category of response (SAP: sensitivity 94%, specificity 79%; PAP: sensitivity 53%, specificity 57%).

An SAP "flare" was associated with response in 8 of 12 patients. An increase in SAP at 1 month is therefore a poor guide to progressive disease and should not be used in isolation to discontinue treatment early.

The SAP profile is of value as an earlier predictor of response than X-rays or bone scans and is more realiable than the PAP profile in monitoring patients with prostate cancer and bone metastases.

Primary endocrine treatment of metastatic prostate cancer yields a response rate approaching 80% (Bailar *et al.*, 1970; Byar, 1973). After relapse, second-line hormonal manipulation or cytotoxic therapy produce responses in only 10 to 30% of patients and usually the median survival is only 4 to 6 months (Johnson *et al.*, 1977; Raghavan, 1988). It has been suggested that responders may have prolonged periods of objective and subjective improvement, although this may alternatively reflect the innate characteristics of the tumour itself without treatment (Tannock, 1985). Accurate prediction and assessment of response is therefore important to allow second-line treatment to be continued where appropriate, but to avoid prolongation of therapy for patients who are not deriving benefit from it. This is particularly important as the side effects from many second-line hormonal or cytotoxic agents are considerable (Crombie *et al.*, 1987; Harnett *et al.*, 1987; Raghavan, 1988). Skeletal X-rays and isotope bone scans are often inconvenient and usually reflect the response to treatment after a substantial delay.

We assessed the predictive value of serum alkaline phosphatase and prostatic acid phosphatase (measured at 0, 1 and 2 months from commencement of therapy) for response in prostate cancer as determined at 3 months using the criteria of the National Prostatic Cancer Project (NPCP) (Slack *et al.*, 1984) (Table 1). In particular, we tried

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to determine whether SAP or PAP can be used as earlier predictors of tumour response or as alternatives to more complex investigations.

Patients and Methods

Selection of Patients

Fifty-one patients undergoing second-line treatment for advanced prostate cancer, and who satisfied the following criteria, were studied: (i) failure or relapse after primary hormonal therapy; (ii) symptomatic bone metastases confirmed on skeletal X-ray or isotope bone scan or both; (iii) no evidence of hepatic metastases (*i.e.* no abnormal hepatic computed tomography [CT] or elevated gamma glutamyltranspeptidase or transaminases [to avoid misinterpretation of the significance of SAP]); (iv) SAP levels recorded for 0, 1 and 2 months. In 31 of these patients PAP levels at 0, 1 and 2 months were also available. All patients were participants in phase II trials of second-line hormonal therapy (aminoglutethimide or megestrol acetate) or cytotoxic chemotherapy being conducted at our institution (the details of response and toxicity having been reported elsewhere) (Crombie *et al.*, 1987; Harnett *et al.*, 1987; Raghavan, 1988).

Table 1

Partial Response (PR)

Any of the following criteria

1. Recalcification of 1 or more of any osteolytic lesions.
2. A reduction by 50% in the number of increased uptake areas on the bone scan.
3. Decrease of 50% or more in cross-sectional area of any measurable lesions.
4. If hepatomegaly is a significant indicator, there must be at least a 30% reduction in liver size indicated by a change in the measurements, and at least a 30% improvement of all pre-treated abnormalities of liver function, including bilirubin and SGOT.

All of the following:

5. No new sites of disease.
6. Acid phosphatase returned to normal.
7. No deterioration in weight (> 10%), symptoms or performance status.

Objectively Stable (SD)

All of the following criteria:

1. No new lesions occurred and no measurable lesions increased by more than 25% in cross-sectional area.
2. Elevated acid phosphatase, if present, decreased, though need not have returned to normal.
3. Osteolytic lesions, if present, did not appear to worsen.
4. Osteoblastic lesions, if present, remained stable on the bone scan.
5. Hepatomegaly, if present, did not appear to worsen by more than a 30% increase in the measurements, and symptoms of hepatic abnormalities did not worsen, including bilirubin and SGOT
6. No significant cancer-related deterioration in weight (> 10%), symptoms or performance status

Seventeen additional patients who were participants in these trials failed to meet these criteria: no bone metastases (1 patient); evidence of liver metastases (2); missing SAP levels (11); inevaluable for response (3). Of the 11 patients with missing SAP values, 9 had progressive disease, 1 stable disease and 1 partial response. The implications of these exclusions are discussed later. An additional analysis including patients with liver metastases gave results almost identical to those reported (data not shown).

Definition of Response Criteria and Enzyme Tests

Partial response, stable disease and progressive disease were determined at 3 months using NPCP criteria (Slack *et al.*, 1984). It was deemed important to determine prior to entry into the phase II trials that patients had objectively progressive disease (usually accompanied by pain or other symptoms) to reduce the risk of misinterpreting the classification of stable disease as a form of response. For this study, patients were divided into 2 groups—those apparently deriving objective benefit ("response") from therapy (partial response, PR; disease stabilisation, SD) and those with progressive disease (PD). For these 2 groups, enzyme profiles were defined, based on the SAP and PAP levels at 0, 1 and 2 months. These profiles at 1 month were defined thus: "increased": SAP/PAP level increased by ≥15% of baseline level; "stable": change in SAP/PAP level of <15% of baseline level; "decreased": SAP/PAP level decreased by ≥15% of baseline level.

The same definitions were used at 2 months, provided that the levels did not fall within an additional category ("flare"), defined as an increase of ≥15% of baseline level at 1 month followed by a fall at 2 months of ≥15% of the 1-month level. There were no patients in whom the levels decreased at 1 month and then increased at 2 months.

SAP was measured on an American Monitor Parallel Analyzer, using p-nitrophenylphosphate substrate at pH 10.2. The resulting coloured complex was measured at 410 nm. At a level of 103 u/l the coefficient of variation (CV) is 2.4% and at a level of 253 u/l the CV is 1.2%. A solid phase enzyme immunoassay kit (Abbott Laboratories, Sydney) was used to measure PAP. This double antibody assay requires horseradish peroxidase conjugation with subsequent colour development using ortho-phenyl diamine substrate. The resulting coloured complex is measured at 492 nm. At a level of 1.9 ng/ml the CV is 8.2% and at 13.5 ng/ml the CV is 8.9%.

Statistical Methods

The association between the enzyme profiles and response categories was compared using a generalised Fisher's exact text for r × c contingency tables (Mehta and Patel, 1983). In using the enzyme profiles to predict tumour response, the profiles were first placed in order as "increased", "stable", "flare" and "decreased" (*i.e.* moving progressively from categories least likely to indicate response towards categories most likely to indicate tumour response). For a simple test of tumour response, "decreased" and "flare" profiles were classified as positive for predicting response while "stable" or "increased" profiles were classified as negative. Based on this cut-off (*i.e.* between "stable" and "flare"), *sensitivity* refers to the likelihood of obtaining a positive test result ("decreased" or "flare" profiles) in a patient who "responds" (PR, SD). *Specificity* refers to the chance of a negative test result ("stable" or "increased" profiles) in a patient who does not "respond" (PD). Alternative cut-off levels (*e.g.* between "increased" and "stable" profiles) would lead to different definitions of sensitivity and specificity. The initial choice of cut-off defined here is somewhat arbitrary and not based on biological criteria.

Performance of Tests using ROC Curves

A useful method of examining the performance of different tests in predicting response is to use ROC (receiver operating characteristic) curves (Weinstein *et al.*, 1980) which do not require a simple cut-off to be specified between positive and negative results. An ROC curve is essentially a plot of the true positive rates (sensitivity) against the false positive rates (1-specificity) using all different possible cut-offs for determining a positive and negative test. In the present study, 3 different cut-offs were possible, as described in detail in the legend to the Figure. The ROC curves in the Figure illustrate the performance of SAP and PAP profiles at 2 months for predicting response. Curves with a higher sensitivity and specificity for various cut-offs will be closer to the top left-hand corner of the graph, whilst a 45° line (dotted line in the Figure) indicates a test with no discriminant value. The ROC curve provides a simple and graphical means of comparing 2 tests with the better test plotted closer to the top left corner. Furthermore, the ROC curve can be used to obtain sensitivity and specificity of the test for any given cut-off. The area under the curve is a measure of the test's performance. A comparison of areas under the ROC curves was undertaken using the method of Hanley and McNeil (1982, 1983).

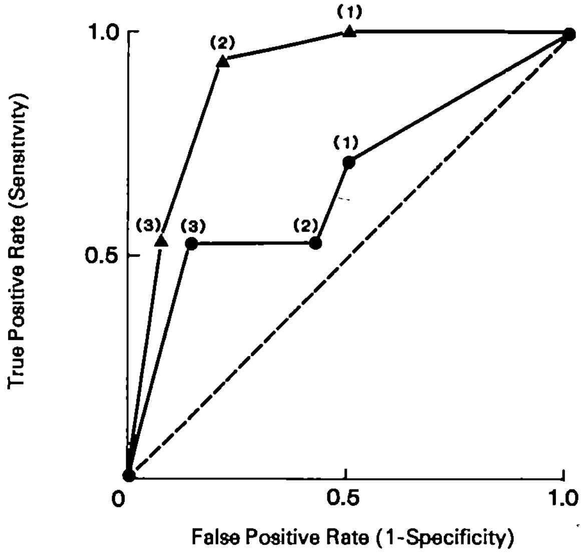

Fig. Area under ROC curve indicating performance of SAP and PAP profiles to predict tumour response ▲——▲ SAP Area under curve = 90.1% ± 5 8 (SE) ●——● PAP Area under curve = 66.0% ± 9 9 (SE). The area under SAP curve is significantly greater ($P=0.025$). The ROC curve is a plot of sensitivity versus (1-specificity) for different cut-offs, *viz*: (1) "Increased" versus "stable", "flare" and "decreased". (2) "Increased", "stable" versus "flare" and "decreased" (3) "Increased", "stable" and "flare" versus "decreased". The figure can also be used to determine sensitivity and specificity of the SAP (and PAP) profiles at different cut-offs, *e g* for cut-off (1), sensitivity = 100% and specificity = 50%; for cut-off (3), sensitivity = 53% and specificity = 93%.

Results

Of the 51 patients, 45 (88%) had elevated SAP levels at the start of treatment. PAP was elevated in 29 of the 31 patients (94%); 24 patients (47%) showed objective "benefit" from therapy, in that 1 patient had PR and 23 SD by NPCP criteria (Slack *et al.*, 1984). Table 2 outlines the response categories and SAP and PAP profiles at 1 and 2 months. It is clear that the strongest association between profile and response category is for SAP at 2 months ($P=0.00001$). It can also be seen that an elevation of SAP at 1 month is a poor guide to whether patients

Table 2 SAP and PAP Profiles at 1 and 2 Months by Response Category

Test	Time (months)	Response category*	Profile				P value†
			Increased	*Stable*	*Flare*	*Decreased*	
SAP	1	PR, SD	8‡	6		10	
		PD	13	12		2	0.02
	2	PR, SD	0 (0%)	4 (50%)	8‡ (67%)	12 (86%)	
		PD	17	4	4	2	0.000001
PAP	1	PR, SD	4	7		6	
		PD	9	2		3	0.10
	2	PR, SD	5 (42%)	3 (75%)	0 (0%)	9 (82%)	
		PD	7	1	4	2	0.02

* PR, SD = "response"; PD = "non response" (PR = partial response, SD = stable disease, PD = progressive disease).
† 2-sided P value based on r × c exact test.
‡ The 8 patients, who had an "increase" in SAP at 1 month and subsequently responded, all showed a "flare" at 2 months.

will ultimately progress. In 12 of these patients (57%), SAP levels subsequently fell ("flare") and this fall was associated with tumour response in 8.

From the data in Table 2 for SAP at 2 months it is clear that both "flare" and "decreased" profiles are more likely than the other profiles to predict tumour response, with response rates of 0, 50, 67 and 86% for the respective profiles "increased", "stable", "flare" and "decreased". This suggests that this order is an appropriate one for using the results in predicting response.

With regard to PAP, there is a weaker association with response categories ($P = 0.02$). This is not just due to the smaller number of patients, as SAP for this subset was still strongly associated with response ($P = 0.0001$). It is of interest that Table 2 shows an elevated PAP at 2 months in 5 responding patients. These patients satisfied all of the other NPCP response criteria in which an increase in PAP alone is not an indicator of PD.

Using SAP and PAP profiles of "decreased" and "flare" to predict response, the sensitivity and specificity and predictive values of these assays are illustrated in Table 3 for the 31 patients with complete data. This demonstrates the much better performance of SAP in predicting response categories. Part of the poor performance of PAP using these criteria is because a PAP "flare" was not associated with subsequent response.

Finally, the performances of these 2 tests using the profiles at 2 months were compared using ROC curves (see legend to Figure). The area under the curve for SAP (90.1%) is significantly greater than that for PAP at 66.0% ($P = 0.025$), indicating that it is the better test. For cut-off level [1] ("decreased", "flare" and 'stable" {positive} versus "increased" {negative}), the sensitivity of SAP is 100% but the specificity is only 50%. Cut-off level [2] ("decreased" and "flare" {positive} versus "increased" and "stable" {negative}) minimises the false positive and false negative errors and is the cut-off level used in Table 3.

A comparison of the two tests was also made using the profiles at 1 month, where the area under the curve for SAP is 56.5% ± 10.5 (SE) and for PAP 68.5% ± 10.0 (SE). These differences are not statistically significant ($P = 0.39$). The poor discriminative ability of SAP at 1 month compared with SAP at 2 months is largely due to those patients with an increased level at 1 month who had a "flare" profile at 2 months.

Discussion

In advanced prostate cancer, SAP appears to be a more sensitive index of bone metastases than PAP (Urwin *et al.*, 1985). Merrick *et al.* (1985) demonstrated that a raised SAP is a more important

Table 3 Predictive Values of SAP and PAP at 2 Months for Response Categories (n = 31)

Item	Test	
	SAP (%)	*PAP (%)*
Sensitivity	94	53
Specificity	79	57
Predictive value positive*	84	60
Predictive value negative†	92	50

* Probability of response (PR, SD) given SAP or PAP profile positive ("flare", "decreased").
† Probability of PD given SAP or PAP profile negative ("increased", "stable").

predictor of survival than bone scans. Furthermore, Bishop *et al.* (1985) reported that response to primary hormonal therapy is more readily demonstrated with serial measurement of SAP than with serial bone scans. In this report it was concluded that serial follow-up bone scans were unnecessary, although these data were not presented using standard criteria of response.

Methods for calculating sensitivity, specificity and ROC curves have been traditionally used in the evaluation of diagnostic tests (for classifying patients as "positive" or "negative" for a disease) (McNeil *et al.*, 1975; Weinstein *et al.*, 1980; Hanley and McNeil, 1982, 1983). However, these methods are equally valid in evaluating the performance of tests for predicting outcomes such as response to treatment, as presented in this report. In particular, the ROC curve is a useful method for displaying graphically the relative performances of different predictive tests where the optimal cut-off for classifying a test result as positive or negative is unclear.

The results in the Figure indicate that changes in SAP are significantly more accurate in predicting response than the corresponding PAP levels. Of particular importance, an SAP "flare" should be noted carefully as it occurred in 8 (33%) of the patients who responded to treatment. Thus an elevated SAP at 1 month does not necessarily indicate a need to discontinue treatment early.

A limitation of this study is its retrospective nature and the problems of patient selection. For example, a greater proportion of excluded patients with missing biochemical data had progressive disease, and thus the positive predictive values are somewhat over-estimated, while negative predictive values are under-estimated. It should also be noted that while SAP is strongly predictive for objective response according to the criteria of the NPCP (Table 1), most "responders" were in the category of objective stabilisation. The validity of this category as an indicator of response to treatment has been questioned (Eisenberger *et al.*, 1985; Tannock, 1985). Nevertheless, as shown in Table 1, the criteria of the NPCP require that there be no increase of symptoms (if present) to qualify for "stable disease", and thus may represent at least a degree of benefit for the patient who was deteriorating before the commencement of treatment. In addition, we attempted to exclude patients with stable disease from entry into the phase II studies from which the data for this report were extracted, as outlined above.

Since we have shown that the SAP profile is a more accurate predictor of response than is PAP, we believe there is a need for reappraisal of those classifications of response that incorporate only PAP as the major biochemical feature. Furthermore, as suggested by others, the validity of a response classification depends on how it correlates with other relevant end-points of treatment, such as duration of survival, time to progression and the quality of life experienced by the patient. Our current research programme includes an attempt to define new criteria of response and to assess their ability to predict some of these other end-points. In addition, we are evaluating serial measurement of prostate specific antigen (PSA) and its relationship to other markers of prostate cancer as a prognostic determinant.

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The Authors

J Mackintosh, FRACP, formerly Senior Registrar, Department of Clinical Oncology, Royal Prince Alfred Hospital. Now Consultant Oncologist, Mater Hospital, Brisbane

J. Simes, SM, MD, FRACP, Medical Oncologist, Department of Clinical Oncology, Royal Prince Alfred Hospital and Director, NH and MRC Clinical Trials Centre, University of Sydney.

D. Raghavan, PhD, FRACP, Research Director, Urological Cancer Research Unit

B Pearson, FRCS, FRACS, Visiting Urologist, Department of Urology, and Chairman, Urological Cancer Research Unit

Requests for reprints to D Raghavan, Urological Cancer Research Unit, Missenden Road, Camperdown, NSW 2050, Australia

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Comparison of Primary Orchiectomy and Polyoestradiol Phosphate in the Treatment of Advanced Prostatic Cancer

R. HAAPIAINEN, S. RANNIKKO, O. ALFTHAN and the FINNPROSTATE GROUP

Second Department of Surgery, Urological Unit, Helsinki University Central Hospital, Helsinki, Finland

Summary—The primary clinical efficacy of orchiectomy and polyoestradiol phosphate (PEP) 160 mg/month i.m. was evaluated by progression and cancer mortality rates in a Finnish multicentre study comprising 200 prostatic cancer patients. After the minimum follow-up time of 2 years there was a significant difference between the groups—orchiectomy delayed progression of the disease more effectively. The follow-up time is rather short for prostatic cancer, but on the basis of this preliminary study the dose of PEP seems to be insufficient in the treatment of advanced prostatic cancer.

Endocrine therapy is effective in retarding prostatic cancer growth in 70 to 80% of cases (Scott *et al.*, 1980). Although it is still uncertain whether endocrine therapy influences overall survival, it is obvious that some patients enjoy a prolonged symptom-free life after endocrine palliation; a disease-free interval may last some years. In Finland, orchiectomy has traditionally been the treatment of choice; in the Scandinavian countries PEP has been another common treatment (Jönsson, 1977). Previously, PEP was given at a dosage of 80 mg/month in combination with oral ethinyloestradiol, but during recent years the dose has been doubled and PEP has been used alone in advanced cases.

The purpose of the present study was to compare the clinical efficacy of orchiectomy and PEP (160 mg/month) in patients with advanced prostatic cancer.

Patients and Methods

The series comprised 200 patients with prostatic carcinoma verified histologically and/or cytologically between January 1985 and March 1987 in 9 Finnish hospitals. The exclusion criteria were: previously treated prostatic cancer, history of acute thromboembolic episode, non-respondent decompensated cardiac insufficiency, severe liver disease, daily use of acetosalicylic acid (ASA), allergy to ASA and anticoagulant therapy.

The patients were randomised into 2 treatment groups, the orchiectomy group comprising 75 patients (mean age 72.6 years) and the other 125 patients (mean age 70.7 years) given PEP (Estradurin) 160 mg/month. The imbalance between the groups was due to the trial design, according to which oestrogen-treated patients were randomised to receive in a double-blind manner either oral ASA (75 mg) or placebo during the first 6 months of oestrogen therapy. The results of the possible inhibitory effect of daily low dose ASA on cardiovascular complications during the high risk early phase of oestrogen therapy have been reported previously (Aro *et al.*, 1989).

At the time of diagnosis there were no significant differences between the orchiectomy and oestrogen groups in terms of local extent of tumour (T classification), presence of distant metastases (M classification) or histological differentiation grade of the malignancy (G classification) (Table 1).

The patients were examined 3, 6 and 12 months after the start of treatment and thereafter every 6 months. Apart from regular assessment visits, examinations were performed whenever symptoms indicated progression. The same criteria were applied to all patients in the evaluation of response to treatment. Progression of disease was evaluated

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Table 1 Extent of Primary Tumour (T classification), Presence of Distant Metastases (M classification) and Differentiation Grade (G classification) in Patients with Prostatic cancer by Treatment Groups

Therapy	*No. of patients*	*T0–2*	*T3–4*	*M0*	*M1*	*G1*	*G2*	*G3*
Orchiectomy	75	7	68	47	28	15	45	15
Oestrogen	125	10	115	66	59	30	82	13

Table 2 Progression and Cause of Death in Orchiectomised and Oestrogen-treated Patients with Carcinoma of the Prostate

Therapy	*No of patients*	*Progression*	*Cancer death*	*Cardiovascular disease*	*Other reason*
Orchiectomy	75	16	5	1	0
Oestrogen	125	51	6	2	4

according to the SPCG (Scandinavian Prostatic Cancer Group) criteria (Aro *et al.*, 1989), a modification of the EORTC criteria (Schroeder, 1984). Progression was defined as an increase in prostatic tumour size of more than 25% and/or an increase in the size of metastases of more than 25%, or appearance of new metastases. Progression was not based on changes in prostatic acid phosphatase or performance status only.

Statistical analysis of proportions was done using the χ^2 test and the test for linear trend. Survival analyses were performed by the conventional product limit method and the Cox proportional hazard method. The term "non-progression" indicates disease-free interval. The response criteria used were progression of disease as defined above and cancer death which was registered during the primary therapy form, *i.e.* the disease was progressing very rapidly and was so aggressive that the patient died during evaluation of the progressive state.

Results

During the first 2 years, which is the minimum follow-up time, 16 of 75 orchiectomised patients (21%) showed evidence of progression and another 5 (7%) had such aggressive disease that they died of disseminated prostatic cancer during the evaluation phase. In the oestrogen group, 51 of 125 patients (41%) showed progression and, in addition, 6 patients (5%) died from prostatic carcinoma.

One patient in the orchiectomy and 2 in the oestrogen group died from cardiovascular disease. For other reasons 4 oestrogen-treated patients died (1 suicide, 2 pneumonias and 1 uraemia not related to the basic disease). The progression and mortality rates are presented in Table 2.

The cumulative non-progression curve (Fig. 1) demonstrates all of the progression events in both treatment groups (16+5 orchiectomised and 51+6 oestrogen-treated patients). There was a statistically significant difference ($P = 0.004$) between the groups overall; orchiectomy was more effective in delaying progression of disease.

Some differences were also observed in respect to M categories. Among M0 patients (Fig. 2) the difference between the groups was statistically significant ($P = 0.009$), orchiectomy being more effective. The same trend was seen among M1 patients (Fig. 3). The effect was seen later, however, and the difference was not statistically significant ($P = 0.300$).

Discussion

This is the first prospective, randomised prostatic cancer study in which PEP 160 mg/month is compared with orchiectomy. The results are surprising: significantly more progression of disease was observed in the oestrogen-treated patients

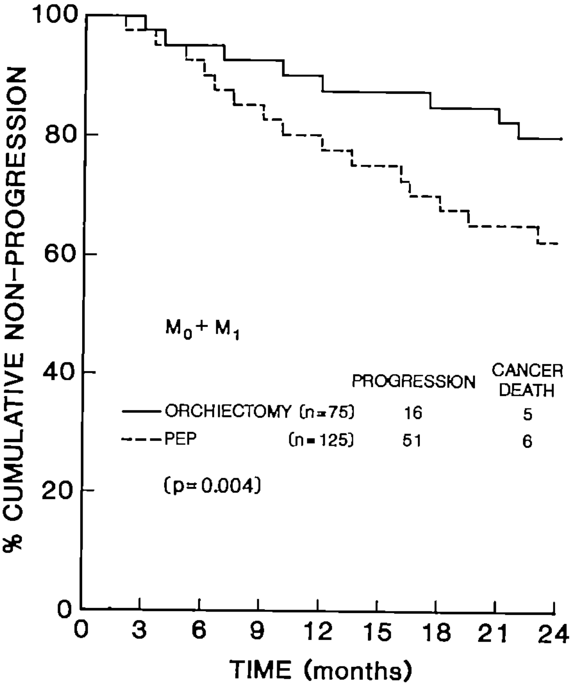

Fig. 1 Cumulative non-progression curve of patients with prostatic carcinoma treated by oestrogen or orchiectomy.

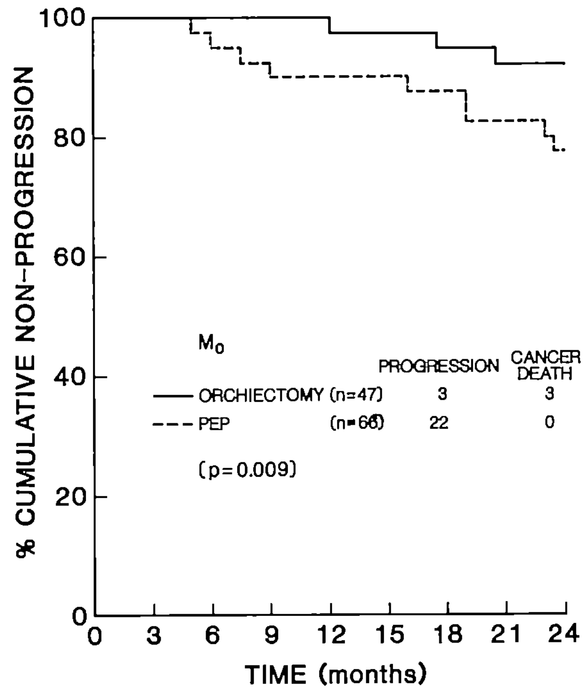

Fig. 2 Cumulative non-progression curve of M0 patients treated by oestrogen or orchiectomy.

during the first 2 years of therapy. Among M0 patients this difference was clearer and it began to appear after the first 6 months. The same trend was noted among M1 patients, but at a later phase. This may reflect the fact that it is easy to define progression when metastasis is verified in a patient who primarily belonged to the M0 category, but progression of disease among M1 patients may sometimes take longer, and control visits are needed to confirm the progression. Even if the minimum follow-up is only 2 years, the difference in clinical efficacy between the 2 treatment regimes is so clear that it cannot be denied. Further investigation is warranted to find an explanation.

Considering the results of our previous investigation (Haapiainen *et al.*, 1986) and the present study, one of the main observations is that there is no essential difference in progression and survival rates between the orchiectomised patients in this study and those in the earlier study (2-year report).

In the previous study, orchiectomy was performed in 131 patients; in the present study 75 patients underwent the procedure. At the time of diagnosis there were no significant differences between these 2 series in terms of local extent of tumour, histological differentiation grade of malignancy and presence of metastases. The mean age of the patients was the same; as was the composition of the study group, and the same criteria were applied in both studies. Thus it is not surprising that the percentage of orchiectomised patients who were progression-free in these 2 studies was very much the same.

When the 2 forms of oestrogen therapy: (1) combination of intramuscular polyoestradiol phosphate (PEP) 80 mg monthly and oral ethinyloestradiol (EE) 0.15 mg/day versus (2) PEP 160 mg/month, were compared with orchiectomy, there was a difference slightly in favour of the combination of intramuscular PEP + oral EE in the previous study. In the present study, significantly more progression of disease was observed in the group treated with PEP 160 mg monthly.

What is the explanation for this? Small, insignificant random variations in the local extent of tumour, histological differentiation grade of malignancy or the presence of metastases do not explain the differences in the clinical efficacy between the oestrogen-treated patients (146 vs 125 patients). The Cox proportional hazard method is valid for analysis of data and it shows that the effect of therapy form is more significant than any other of the factors mentioned above.

The prognostic value of the 2-year analysis in the

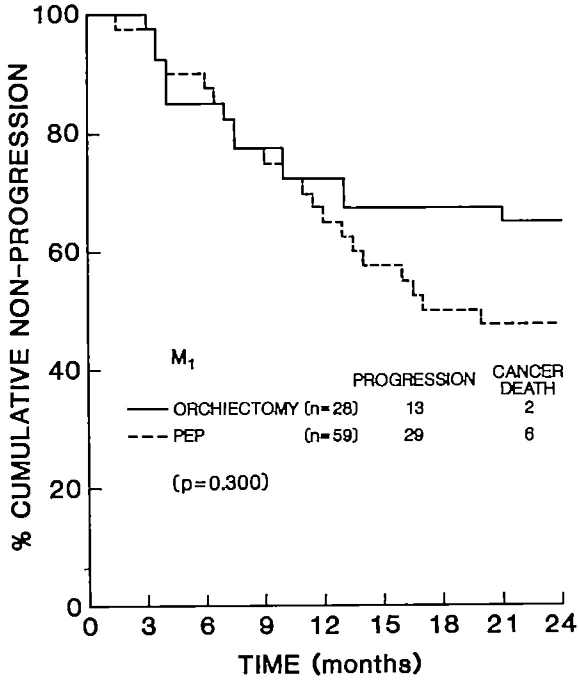

Fig. 3 Cumulative non-progression curve of M1 patients treated by oestrogen or orchiectomy.

previous study (Haapiainen *et al.*, 1986) seemed to be reliable; the respective difference in clinical efficacy between the treatment groups has been confirmed by later analyses (data to be published later). Even if the combination of PEP and EE delayed cancer progression more effectively than orchiectomy, the risk of early phase cardiovascular side effects was also noticeable in the oestrogen group. There is evidence that cardiovascular side effects of oestrogen therapy are specifically related to the oral route of administration (Stege *et al.*, 1987a).

Considering the results of our previous investigation (Haapiainen *et al.*, 1986) and the present study, the main question is whether the monthly dose of 160 mg PEP is sufficient to maintain the serum testosterone level low enough.

In the study by Norlen *et al.* (1987), the steady state plasma concentrations of testosterone were reduced to 45, 25 or 15% of the pre-treatment concentrations in response to PEP 80, 160 and 240 mg every 4 weeks, respectively. No castration levels of testosterone were achieved even with the highest dose of PEP (240 mg/month); the difference in testosterone levels was smaller for the biologically active testosterone, *i.e.* the free fraction, than the total testosterone. However, it was concluded that PEP (160 or 240 mg/month) induced a substantial reduction in plasma testosterone values and that it would be sufficient to give a clinically good therapeutic response. When the dose of PEP is raised to 320 mg/month the testosterone level can be suppressed to castration level (Stege *et al.*, 1987a).

The combination of intramuscular PEP (80 mg/month) and oral ethinyloestradiol 0.15 mg/day) does, however, suppress serum testosterone to castration level. This combination reduces testosterone levels more effectively than PEP alone at a dosage of 160 mg every 4 weeks (Stege *et al.*, 1987b).

The antitumour activity of oestrogens in prostatic carcinoma is based mainly on the decrease in circulating androgens (Huggins and Hodges, 1941). Since regression of prostatic carcinoma can be achieved clinically without maximal suppression of plasma testosterone levels (Scott *et al.*, 1980), it has been proposed that oestrogens have a kind of cytotoxic effect on the tumour tissue (Susan *et al.*, 1976). However, our present clinical results of PEP monotherapy (160 mg/month) do not support this view.

In conclusion, PEP 160 mg/month is clinically insufficient in the treatment of advanced prostatic cancer. The reason may be that the dosage is too low to maintain serum testosterone at a castration level. Orchiectomy is still an important method for treating patients with locally advanced or metastatic prostatic carcinoma. It is effective in reducing serum testosterone, which is the main goal of endocrine therapy in prostatic cancer. It is also inexpensive and does not require frequent hormone determinations. Acceptance of the procedure by the patients is not a problem in northern countries.

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The Authors

R. Haapiainen, MD, Consultant Surgeon and Assistant Lecturer
S. Rannikko, MD, Senior Consultant in Urology.
O. Alfthan, MD, Professor of Urology.

Requests for reprints to: R. Haapiainen, Second Department of Surgery, Helsinki University Central Hospital, Haartmaninkatu 4, SF-00290 Helsinki, Finland.

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Case Reports

Severe Allergic Reaction to an Intraurethral Lignocaine Preparation Containing Parabens Preservatives

T. W. CARR, Department of Urology, Freeman Hospital, Newcastle upon Tyne

Adverse reactions to intraurethral lignocaine have been noted previously, although they are rare. Two cases are now presented of severe anaphylaxis probably related to parabens preservatives in the lignocaine preparation used.

Case Reports

Case 1

A total of 11 ml of "Instillagel" (Farco-Pharma) were introduced into the urethra of an 80-year-old man. This preparation contains 2% lignocaine, 0.25% chlorhexidine and the parabens preservatives methyl p-hydroxybenzoate 0.06% and propyl p-hydroxybenzoate 0.025%. A penile clamp was then applied for 5 min. Shortly after flexible cystoscopy the patient collapsed. His blood pressure was 50/30 mm Hg. A widespread macular rash developed accompanied by marked periorbital oedema. There was no bronchospasm. He responded well to resuscitative measures. Intraurethral lignocaine without preservatives was administered 2 months later with no untoward effect.

Case 2

The same preparation was used in a 76-year-old man. Following cystoscopy a severe anaphylactic reaction occurred characterised by hypotension and a macular rash. He was successfully resuscitated. In both cases serial ECG and plasma cardiac enzymes were normal.

Comment

Two forms of adverse reaction are possible after the instillation of intraurethral lignocaine. Firstly, sufficient can be absorbed to produce systemic toxic effects such as convulsions (Sundaram, 1987). Secondly, an allergic reaction can occur, as in the patients described here. Allergy to parabens preservatives in lignocaine administered subcutaneously has been reported (Swanson, 1983). Although a severe anaphylactic reaction to methyl parabens in rectal lubricating jelly has been recorded (Jones, 1988), there have been no reports of a similar reaction after intraurethral administration.

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Requests for reprints to: T. W Carr, Department of Urology, Dudley Road Hospital, Birmingham B18 7HQ.

Bilateral Ureteric Obstruction Secondary to Endometriosis

T. ESEN, M. AKINCI, H. ANDER, M. TUNÇ, S. TELLALOĞLU and I. NARTER, *Departments of Urology and Gynaecology-Obstetrics, University of Istanbul, Istanbul, Turkey*

Case Report

A 23-year-old nulliparous woman presented with lumbar pain, dysuria, dysmenorrhoea and occasional haematuria. IVU demonstrated non-visualisation of the right kidney and a left hydroureteronephrosis with distal obstruction (Fig.). US and CT scans revealed bilateral hydronephrosis, multicystic ovaries and a myomatous uterus. Retrograde pyelography confirmed the right hydroureteronephrosis with no intrinsic obstruction. The patient underwent laparatomy which established the diagnosis of pelvic endometriosis, the ureters being surrounded by retroperitoneal fibrotic tissue. A hysterectomy and bilateral salpingo-oophorectomy with ureterolysis were performed. Histopathological examination revealed disseminated endometriosis. Under oestrogen substitution the bilateral hydronephrosis resolved dramatically and 1 year post-operatively IVU showed normal renal function without obstruction.

Comment

Endometriosis is a common disorder affecting 10 to 20% of menstruating women. Urinary tract involve-

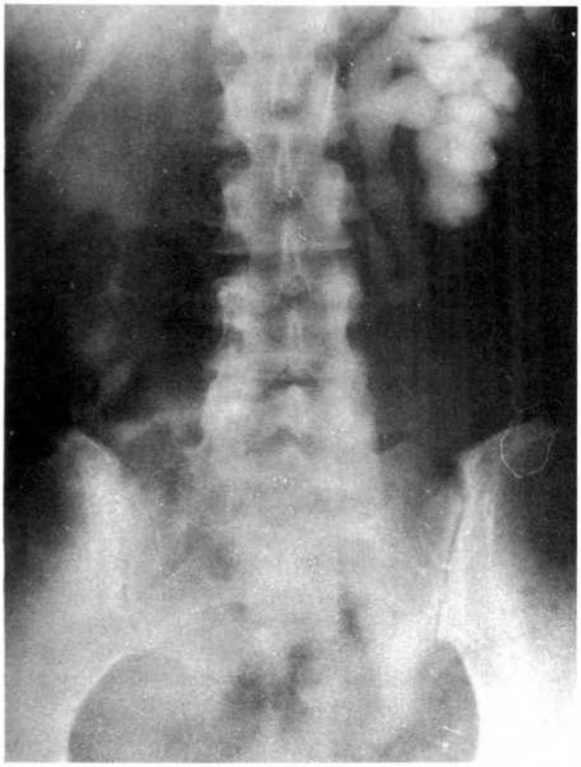

Fig. Pre-operative intravenous urogram showing non-functioning kidney on the right and hydroureteronephrosis on the left.

ment accounts for 1.2% of the cases, with the bladder, ureter and kidney being involved in a ratio of 40:5:1 (Kane and Drovin, 1985; Mourin-Jouret, 1987; Appel, 1988). Ureteric endometriosis is mostly unilateral, bilateral forms accounting for 15 to 20% of all ureteric involvement (Mourin-Jouret, 1987). Arising from pelvic foci of endometriosis, ureteric involvement is due either to contiguous extension or to lymphatic spread and is mostly extrinsic (Kane and Drovin, 1985). Since 25% of kidneys with ureteric obstruction secondary to endometriosis are non-functioning at the time of diagnosis, obstructive uropathy has to be ruled out in patients with proven endometriosis. Optimal treatment includes relief of obstruction, resection of endometriotic tissue and castration. If periureteric fibrosis is present, castration alone will not be helpful and ureterolysis has to be performed. In young and nulliparous patients with mild hydronephrosis, hormonal manipulation can replace surgery (Kane and Drovin, 1985; Appel, 1988) but one has to bear in mind that treating ureteric obstruction with hormonal manipulation alone involves the risk of recurrence and loss of renal function.

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Requests for reprints to: T. Esen, Istanbul Tip Fakültesi, Üroloji Kliniği, Çapa-Istanbul, Turkey.

Pelvic Osteochondroma Causing Haematuria

R. R. PHILLIPS, S. H. LEE and G. M. FLANNIGAN,
Departments of Radiology and Urology, The Middlesex Hospital, London

Microscopic haematuria is a relatively uncommon problem in routine screening health checks. Extensive urological investigation is indicated to elucidate the cause, but sometimes the aetiology remains obscure. We present a case of microscopic haematuria due to a pelvic osteochondroma which was diagnosed initially on plain radiography and computed tomography (CT), but was not fully appreciated until cystoscopy was performed.

Case Report

A 41-year-old Caucasian male was found to have microscopic haematuria on routine testing at a cardiology out-patient clinic. He had no other urological symptoms. The only abnormal finding was a hard mass palpable anteriorly on rectal examination. Urine cytology was negative.

Plain films of the pelvis revealed a cartilage-capped exostosis arising from the superior aspect of the right pubic ramus, which on intravenous urography (Fig. 1) displaced the bladder to the left and on CT (Fig. 2) showed its close relationship to the prostate and bladder base. The upper renal tract was normal.

The bladder at cystoscopy appeared normal but there was an indentation into the right side of the prostatic urethra with prominent mucosal vessels.

The bony lesion was removed through a Pfannenstiel incision. Histologically the lesion was confirmed as a cartilage-capped exostosis (osteochondroma). The patient remains well with no recurrence of his microscopic haematuria on follow-up.

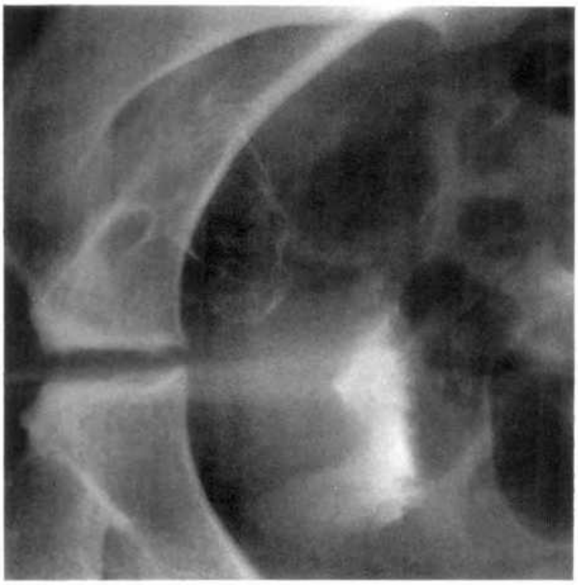

Fig. 1 Intravenous urogram showing the exostosis arising from the right superior pubic ramus and displacing the bladder base.

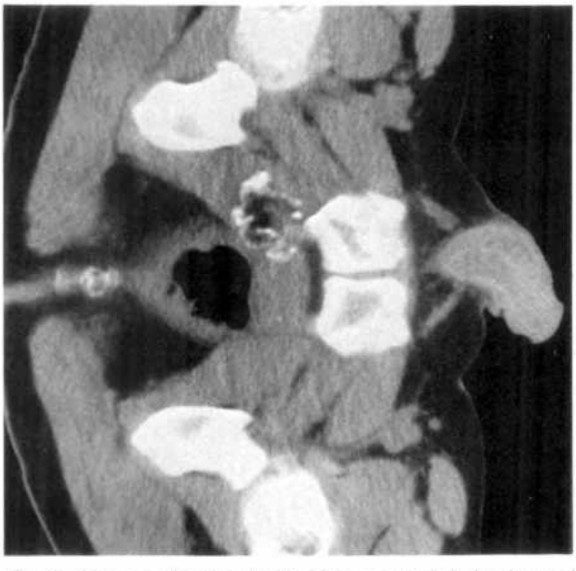

Fig. 2 CT scan showing the tip of the exostosis indenting and compressing the left side of the prostate.

Comment

Osteochondromas are the most common benign growth to affect the skeleton. The age group predilection is 10 to 20 years, with a male:female ratio of 1.4:1. They arise on the metaphysis from aberrant epiphyseal cartilage and migrate down to the diaphysis with growth of the bone. Symptoms may occur due to local pressure on adjacent nerves and vessels or due to mechanical problems. The lesions may be discovered during investigation of a painless mass or more usually as an incidental finding. They arise in both the axial and appendicular skeleton, the commonest sites being around the knee and proximal humerus. Dahlin (1986) recorded an incidence of pelvic osteochondromas in 8% of his series of solitary bone lesions (52 of 640 patients).

The radiological hallmarks of osteochondromas are: (a) The cortex of the exostosis blends with the adjacent normal bone. (b) The cartilage cap ossifies with age to produce punctate or nodular calcification. Extensive calcification may occur with benign lesions.

Malignant degeneration occurs in later life in less than 1% of solitary lesions and the incidence of malignant change rises to 10% in multiple osteochondromata (diaphyseal achalasia).

The features indicating malignant change are rapid growth of a stable lesion (particularly increase in thickness of the cartilaginous cap), a large associated soft tissue mass and invasion with destruction of the exostosis. CT is currently the best imaging modality to demonstrate malignant change, but biopsy in these cases is mandatory. This unusual cause of haematuria due to prostatic compression from an osteochondroma has not been previously described.

Acknowledgement

We are grateful to Mr A. G. A. Cowie for allowing us to present this case.

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Requests for reprints to: R. R. Phillips, Department of Radiology, Middlesex Hospital, Mortimer Street, London W1N 8AA.

Testicular Metastasis from Prostatic Carcinoma

J. O. R. SÖNKSEN, E. F. HANSEN and H. COLSTRUP,
Department of Urology, Rigshospitalet, University of Copenhagen, Denmark

Testicular metastases from prostatic carcinoma are rare and less than 60 cases have been described in the literature. Only 9 of the metastases were discovered clinically and so far all patients with prostatic carcinoma and a clinically verified metastasis to the testis have received oestrogen treatment. We report a patient with prostatic carcinoma stage IV, who was not treated with oestrogen, where clinical examination revealed a testicular tumour that later proved to be of prostatic origin.

Case Report

An 81-year-old man was admitted in 1988 with a history of prostatic carcinoma since 1981, primarily treated at a local hospital with transurethral resection and later bilateral nephrostomies. In February 1987 a bone scan revealed multiple skeletal metastases.

On admission the left kidney was found to be nonfunctioning because of long-standing post-renal obstruction. The function of the right kidney returned to normal on re-establishment of the right-sided nephrostomy. The patient complained of bone pain but otherwise felt well. Physical examination revealed a 3 × 1 cm firm, slightly tender mass in the upper part of the left testis. The right testis was normal.

A radical orchiectomy was performed on the left side and a subcapsular orchiectomy on the right. Gross examination showed a firm tumour measuring 2 × 2 × 2 cm in the left rete testis. Microscopy revealed a well differentiated adenocarcinoma which upon immunohistochemical analysis proved to be of prostatic origin. The right testis was microscopically normal. No further treatment was instituted and at follow-up 6 months later the patient was well.

Comment

Most testicular metastases from prostatic carcinoma are found incidentally at autopsy or following orchiectomy in palliative treatment (McWilliams *et al.*, 1983). Only occasionally do these metastases become large enough to simulate a primary testicular tumour (Marble, 1960). It is suggested that oestrogen treatment makes the testes more susceptible to invasion (Silverton, 1976). Others believe that the oestrogen treatment has lengthened the survival of patients with prostatic carcinoma and thereby given more time for widespread metastases to develop (Kay *et al.*, 1954).

The present case illustrates that clinically demonstrable metastases from prostatic carcinoma to the testis can occur without previous oestrogen treatment.

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Requests for reprints to: J. O. R. Sönksen, Sct. Jakobsgade 22, DK-100 Cph. Ö.

Tuberculous Epididymo-Orchitis Following Intravesical BCG

V. K. GEORGE, G. L. RUSSELL, B. D. W. HARRISON and N. A. GREEN, *Department of Urology, Norfolk and Norwich Hospital, and Department of Respiratory Medicine, West Norwich Hospital, Norwich*

BCG immunotherapy is gaining increasing acceptance in the management of a number of bladder transitional cell neoplastic lesions. Mild adverse reactions occur frequently, but the unusual complication of tuberculous epididymo-orchitis is now reported.

Case Report

A 69-year-old man presented with haematuria and was found at cystoscopy to have a solitary G2 Ta tumour. Because of similar tumour recurrences and *in situ* change at regular endoscopic reviews, BCG instillation was commenced 2 years after the initial diagnosis. It was planned to instil 150 mg Pasteur strain weekly over a 6-week period, but 3 days after the second dose the patient

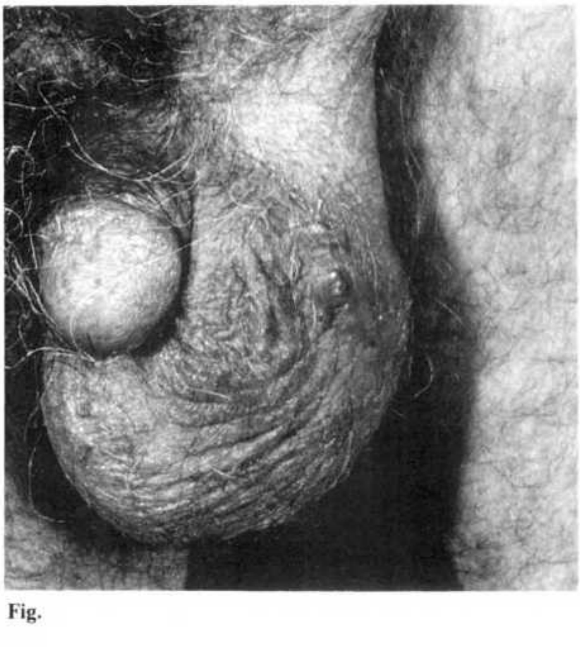

Fig.

developed bilateral testicular pain and swelling. He was commenced on penicillin/clavulanic acid by his family doctor and subsequent BCG treatments were discontinued. A discharging sinus was noted from the left hemi-scrotum 2 months later (Fig.) and cultures from this site confirmed the presence of acid-fast bacilli. Standard anti-tuberculous therapy was instituted and the scrotum explored. A necrotic left testis was removed and an abscess from the right hemi-scrotum drained; both sites contained acid fast bacilli. Histology of the orchiectomy specimen showed extensive granulomatous inflammation of the testis and epididymis with caseous necrosis. Subsequent culture of the pus revealed BCG organisms.

Comment

BCG immunotherapy is effective in the treatment of Ta, T1 and carcinoma *in situ* bladder lesions (Soloway and Perry, 1987). Minor complications, including fever, a 'flu-like illness, haematuria and bladder irritation symptoms are not uncommon (Morales, 1984). Granulomatous lesions in the liver, lungs and prostate are also recorded and 2 cases of granulomatous epididymo-orchitis were reported by Hudson *et al.* (1987). The case described here is unusual as acid fast bacilli have been identified in association with caseous necrosis of the testis following intravesical BCG therapy.

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Requests for reprints to: N. A. Green, Department of Urology, Norfolk and Norwich Hospital, Brunswick Road, Norwich NR1 3SR.

Caecovesical Fistula Secondary to Diverticulitis

B. M. STEPHENSON, R. FAROUK and D. E. STURDY,
Department of Surgery, Royal Gwent Hospital, Newport

Colovesical fistulas are not uncommon and diverticular disease of the sigmoid colon the most common cause. Caecal diverticulitis presents with right iliac fossa pain and patients are usually suspected of having appendicitis. A case of caecal diverticulitis with fistulation to the bladder is described.

Case Report

A 55-year-old man presented with a 2-month history of recurrent urinary tract infections, pneumaturia and low right-sided abdominal pain. Examination revealed a tender mass in the right iliac fossa. Investigations showed a neutrophil leucocytosis and a mixed *Escherichia coli* and enterococcus urinary tract infection. A barium enema (Fig.) suggested a stricture in the distal sigmoid colon and irregularity of the medial wall of the caecum.

At laparotomy a caecal mass infiltrating the bladder, sigmoid colon and anterior abdominal wall was found. A diagnosis of caecal carcinoma was made. A "palliative" right hemicolectomy in continuity with a limited cystectomy was performed. The affected segment of sigmoid colon was successfully separated from the mass with no evidence of a stricture.

Histological examination showed marked chronic inflammation and abscess formation. No granulomata were identified and there was no evidence of malignancy. The appendix was fibrosed but without any evidence of primary suppurative inflammation.

Comment

A solitary caecal diverticulum is an uncommon

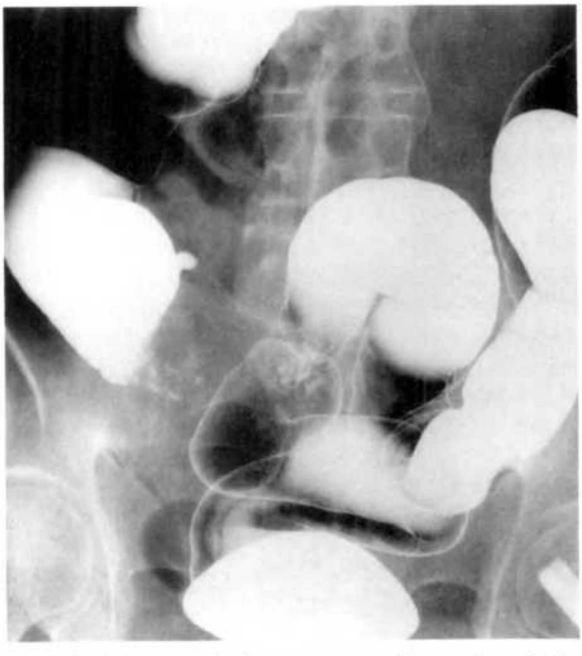

Fig. Double contrast barium enema revealing a stricture in the sigmoid colon and irregularity of the medial wall of the caecum.

finding and generally not associated with diffuse colonic disease. Hughes (1969) reported an incidence of 2.5 to 5% from 200 autopsy examinations.

Caecal diverticulitis usually mimics acute appendicitis, although the patient is often older and has had previous episodes of pain. The inflammatory process is usually localised with fistula formation to the bladder suggested only once before (Case and Shea, 1953).

The barium enema in this case suggested the possibility of metachronous tumours (sigmoid colon and caecum). Though misleading on this occasion, a barium enema is the investigation of choice when caecal diverticula are suspected clinically (Wagner and Zollinger, 1961).

The aetiology of colovesical fistulas is usually determined by cystoscopy and barium enema. In this case histological diagnosis was required.

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Requests for reprints to: B. Stephenson, Coloproctology Research Fellow, Imperial Cancer Research Fund, Genetic Epidemiology Laboratory, 3K Springfield House, Hyde Terrace, Leeds LS2 9LU.

Pseudo-epitheliomatous Hyperkeratotic and Micaceous Balanitis: Evidence for Regarding it as Pre-malignant

M. R. GRAY and I. D. ANSELL, *Department of Urology, City Hospital, Nottingham*

The condition of pseudo-epitheliomatous hyperkeratotic and micaceous balanitis (PKMB) was first described by Lortat-Jacob and Civatte (1961) as a rare, scaling, raised lesion of the glans penis which on histological examination showed acanthosis, hyperkeratosis and pseudo-epitheliomatous hyperplasia.

PKMB is considered benign and in no way premalignant (Rook *et al.*, 1972). This view was reinforced by Mann and Allen (1982) who argued specifically that amputation was too radical a treatment for the condition. Our patient and a comprehensive review of all reported cases (Lortat-Jacob and Civatte, 1961; Bart and Kopf, 1977; Reid and Abell, 1981; Mann and Allen, 1982) provide strong evidence that PKMB has a high propensity for malignant change.

Case Report

A 62-year-old man presented with a lesion on his glans penis. It had started a few months before as a small swelling which he had pricked to reveal pus. At presentation it had scabbed over. He did not complain of pain, discharge or bleeding.

On examination he was noted to be uncircumcised and a hyperkeratotic, scaling, raised lesion was noted on the dorsum of the glans penis. Biopsies (Fig.) showed prominent acanthosis, hyperkeratosis and pseudo-epitheliomatous hyperplasia and some associated inflammation. There was no evidence of carcinoma. The diagnosis of PKMB was made and the patient reassured of the benign nature of the lesion. Low dose irradiation was considered the appropriate treatment and 5000 cGy were given in 30 fractions. Signs of regression were reported 4 months later, but after a further 3 months the lesions had progressed rapidly to an obvious squamous cell carcinoma of the penis requiring partial amputation. There has been no evidence of local or metastatic recurrence 3 months later.

Previous Reports

Lortat-Jacob and Civatte (1961) first described PKMB as an uncommon condition of the glans penis characterised by hyperkeratosis of the glans and an adherent balanitis causing late acquired phimosis. It differed clinically and histologically from balanitis xerotica obliterans and simple penile horn. Six years later they reported that the lesion had undergone malignant change (Lortat-Jacob and Civatte, 1966).

In 1977, Bart and Kopf described an elderly man with biopsy proven PKMB who was treated with topical podophyllin and subsequent curettage and electrodesiccation. Healing failed to occur and repeat biopsies showed low grade squamous carcinoma. The now malignant lesion was treated with 6200 rads and resolved. At the time of the patient's death 3 years later, at the age of 84 from a CVA, there was no evidence of recurrent disease.

In 1981, Reid and Abell attempted to treat PKMB after biopsy with topical keratolytics and antimitotic agents. Regression failed to occur but repeat biopsy confirmed its benign nature; 900 rads were given in an attempt to suppress its proliferation. One year later the patient had an obvious squamous carcinoma and partial amputation was performed.

In 1982, Mann and Allen described a patient who initially presented with phimosis and under-

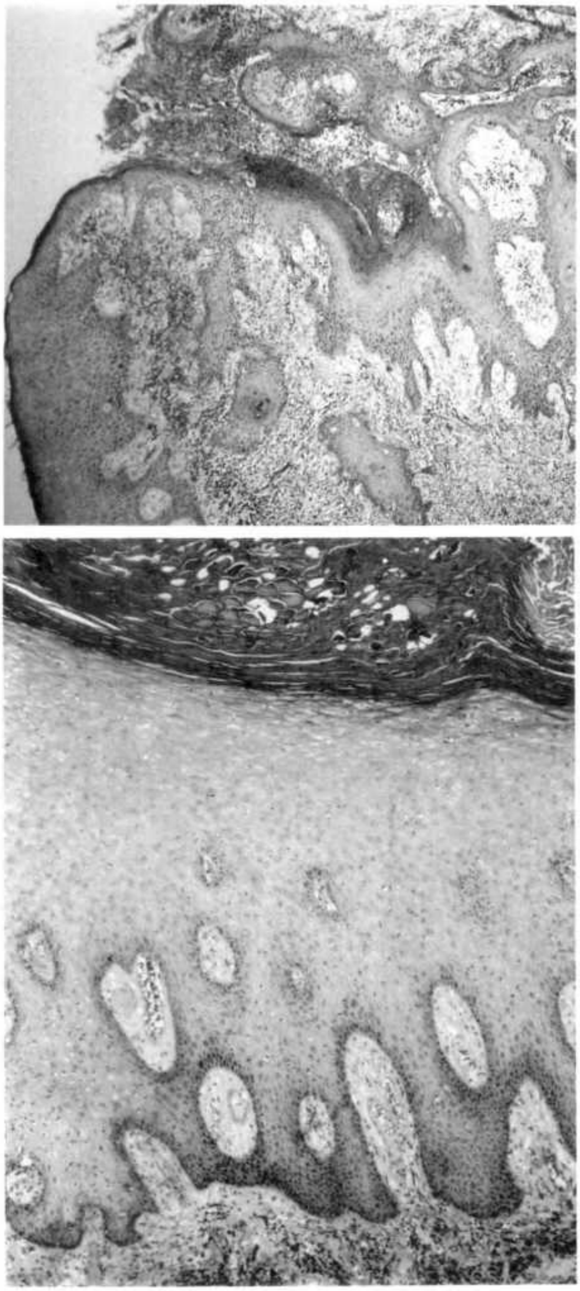

Fig. 1 (A) Infiltrating squamous carcinoma adjacent to acanthotic and hyperkeratotic epithelium. (B) Acanthotic and hyperkeratotic epithelium of PKMB.

went circumcision. Several years later he presented again, complaining of hardening of the glans since the circumcision, and examination showed a micaceous pavement over the glans and warty hyperkeratosis at the sulcus. Biopsy of the sulcus showed pseudoepitheliomatous hyperplasia and a diagnosis of micaceous pseudo-epitheliomatous balanitis was made. Treatment was undertaken by meatal dilatation and meatoplasty. Topical keratolytic, steroids and 5FU ointment were applied but there was no improvement. At the time of reporting, this case remained benign in nature. The authors stated that partial amputation was too radical a treatment for this patient, who was then 46 years old, but since that report the patient has developed squamous carcinoma and has undergone a partial amputation (personal communication).

Comment

Our case of pseudo-epitheliomatous hyperkeratotic and micaceous balanitis is the fifth reported. Each was biopsied at presentation and a benign nature attributed to the lesion. Less than radical treatments were accordingly prescribed. All patients subsequently developed squamous carcinoma, 4 being treated with partial amputation and 1 with radiotherapy.

We conclude that pseudo-epitheliomatous hyperkeratotic and micaceous balanitis is a pre-malignant condition. Topical therapies are ineffective. Low dose irradiation does not alter the course of the disease and one can speculate that it may promote progression to carcinoma.

These patients clearly need close observation, possibly with repeat biopsy to ensure the early diagnosis of malignant change. However, exisional surgery, best achieved by limited partial amputation at the pre-malignant stage, may be the preferred course of action.

Acknowledgement

We thank Mr J. Lemberger, Consultant Urologist, for permission to report this case.

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Requests for reprints to: M. R. Gray, c/o University Department of Surgery, Royal Liverpool Hospital, Prescot Street, Liverpool L7 8XP.

Non-obstructive Hydronephrosis—Baggy and Benign?

A. S. ADAMSON, J. D. ATWELL and D. M. BURGE, *Wessex Regional Centre for Paediatric Surgery, Southampton General Hospital, Southampton*

In 1982 a 3-year-old boy presented with haematuria and urinary tract infection. Investigation showed a slightly full right pelvicaliceal system (Fig.). Vesicoureteric reflux was excluded and DTPA renal imaging failed to demonstrate obstruction.

Investigations were repeated 2, 4 and 6 years later and remained normal, the patient being asymptomatic.

At the age of 15 he presented again with a 12-month history of intermittent loin pain. Investigation confirmed an obstructive hydronephrosis with impaired renal function. An Anderson-Hynes pyeloplasty was performed with relief of symptoms and subsequent improvement of renal function (Fig.).

Discussion

This patient confirms that a non-obstructive hydronephrosis may progress to an obstructing one with subsequent loss of renal function. Repeat DTPA renography with diuretics was unable to predict this change and it is doubtful whether other means of investigating obstruction, namely the Whitaker test (Majd, 1985) or diuretic excretion urography (Whitaker, 1978) would be any more useful. In addition, the former is invasive and the latter unreliable (Whitfield *et al.*, 1977).

There are also important implications for the paediatric urologist, who sees increasing numbers of antenatally diagnosed hydronephrosis. These patients will need regular review and investigation in order to identify those who may be at risk of losing functional renal parenchyma, even in the absence of "radiological obstruction" at presentation.

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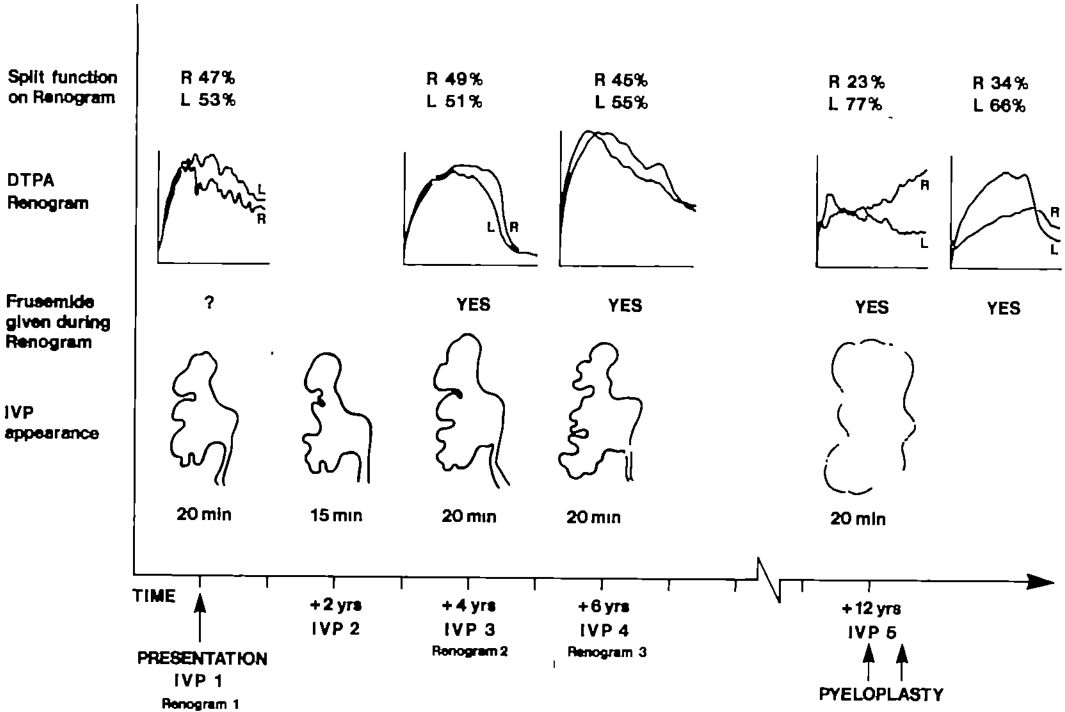

Fig. Diagrammatic representation of the patient's investigations

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Points of Technique

Negative Pressure Induced Erection for the Assessment of Impotent Patients with Peyronie's Disease

D. YACHIA, *Department of Urology, Hillel Yaffe Medical Center, Hadera, Israel*

Peyronie's disease is a benign condition seen in middle-aged men which produces plaque-like thickenings in the tunical albuginea of the corpora cavernosa. In many instances it is accompanied by penile deformity. Some patients may benefit from surgical treatment such as corporoplasty, excision of plaques accompanied by patch grafting and even penile prostheses for penile straightening. As in congenital penile curvatures, documentation of the deformity is required for pre-operative assessment and post-operative comparison. However, some patients have lost their erectile ability and others have unsustained erections and so cannot document their deformity. Thus the technique of negative-pressure treatment for impotence was adopted to evaluate the penile deformity in these patients before deciding upon treatment.

In order to observe penile deformity, Gittes and McLaughlin (1974) introduced the artificial erection, induced by injection of intracavernosal saline with a tourniquet applied around the base of the penis. This is a painful procedure which in most cases should be performed with the patient hospitalised and under anaesthesia. For out-patient assessment of the degree of penile curvature Desai and Gingell (1987) described a method using intracavernosal injections of papaverine and photographic documentation of the erection. They found this technique helpful in patients with Peyronie's disease because the plaques could be palpated and delineated more easily during tumescence. When the erection was complete it was possible to see the distal flaccidity or the fibrotic scarring of the terminal corpora. This technique was criticised by Pryor (1988), particularly when used to assess congenital curvature, because of the potential complications such as prolonged erections; however, it was recommended for the determination of the absence of distal penile erection. Other authors have also advised the use of pharmacologically induced erections for the pre-operative screening of patients who are candidates for plaque excision and patching, and for deciding whether or not a penile prosthesis should be implanted during surgery (Lewis *et al.*, 1988).

During the last 28 months, 36 patients with Peyronie's disease were referred to our "Penile Deformity Service". Notification of appointment was accompanied by a leaflet explaining how to photograph the erect penis in 3 directions. Eleven patients attended without photographs either because they could not achieve an erection at all or the erection was not sustained long enough for the taking of photographs. An artificial erection was therefore induced using the Erec-Aid*, VED (Vacuum Erection Device)† or Pos-T-Vac‡ cylinders. These devices are based on the same principle. A vacuum, applied for 3 to 5 min, causes an erection-like state of the entire penis by suctioning blood into the corpora cavernosa. Penile rigidity was maintained with the help of a constricting band placed around the base of the penis (Fig. 1). The erections were documented by photographs taken in the examination room and the angle of the curvature was measured (Fig. 2). The accuracy of the documentation was controlled by inducing an artificial erection by vacuum in 5 Peyronie's disease patients without erectile problems who did bring their photographs. No significant difference in the deviation angle was found when the angle was measured on photographs taken during erections induced either manually or by vacuum. In none of the 11 patients examined by this technique was the severity of the deformity an obstacle in assessing the deviation angle. One patient with a 45° ventral deviation and another with a 65° dorsolateral angulation were examined without difficulty, although limited space in the vacuum cylinder caused some patients to report pain in the penis, probably because of stretching of the curved penis. The moment the penis was removed from the cylinder with the constricting band at the base it snapped back to its angulated form. No patient complained of flaccidity distal to the plaques. However, in the 11 patients and the 5 controls, satisfactory rigidity of the entire penis was obtained. When potency is in question, papaverine-induced erection can show the adequacy of penile arterial inflow and venous outflow. When the aim is to measure the deviation

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* Erec-Aid, Nu-Potent Inc., Georgia, USA.

† VED, Trans Texas Medical Devices Co., Texas, USA.

‡ Pos-T-Vac, Pos-T-Vac Inc., Kansas, USA.

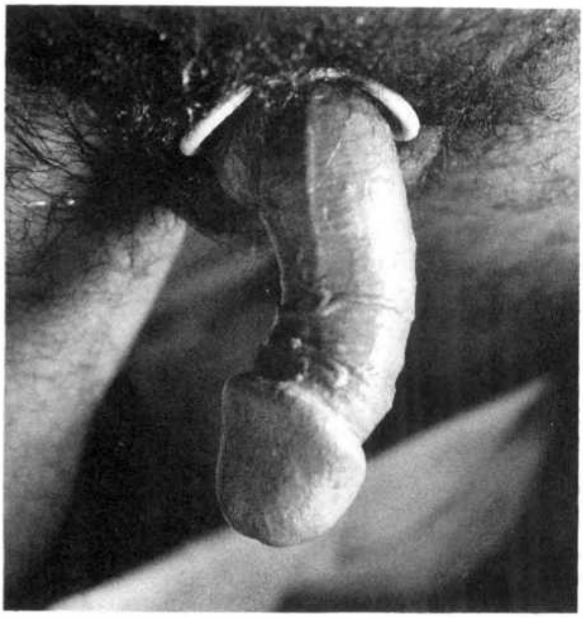

Fig. 1 Penile rigidity is maintained by applying a constricting band at the base of the penis. Note the quality of the erection and the curvature.

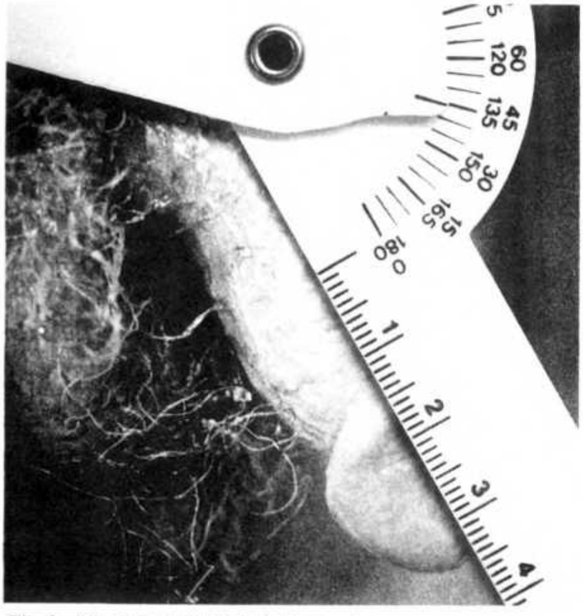

Fig. 2 Measurement of deviation angle.

angle and penile length, the non-invasive negative pressure induced erection can be used safely. Our experience has shown that this is a valuable technique for the assessment of patients with Peyronie's disease who cannot document their curvature or during the first visit of other patients with penile curvature. We recommend it as a safe procedure, except in patients with blood clotting problems, leukemia and sickle-cell disease, because the vacuum may cause petechiae and bruising in these patients.

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Requests for reprints to: D. Yachia, Department of Urology, Hillel Yaffe Medical Center, Hadera 38101, Israel.

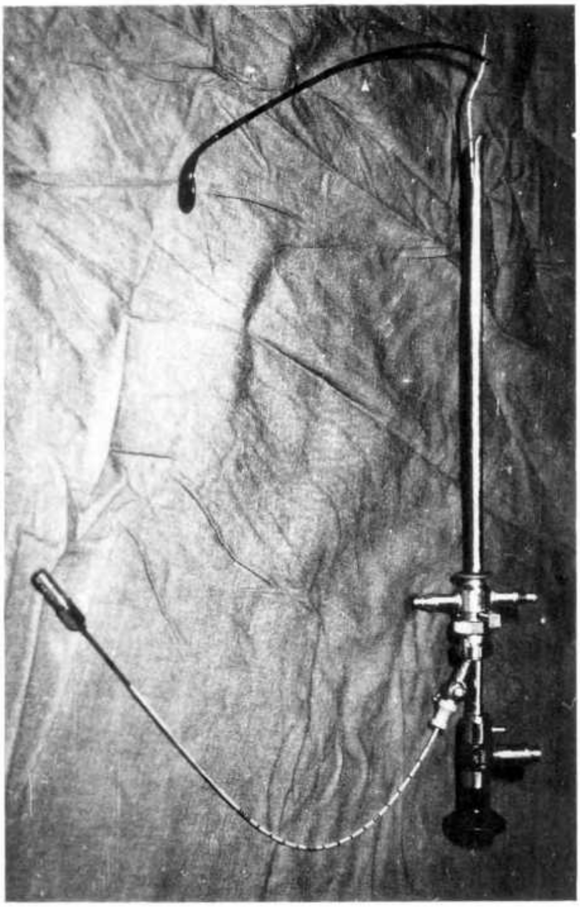
Retrieval of Broken Double-J Catheter by Dormia Basket

I. ERKAN, O. SARIYÜCE and H. ÖZEN, *Department of Urology, Hacettepe University Hospital, Ankara, Turkey*

Case Report

A 34-year-old male patient presented with bilateral obstructing renal stones and underwent right pyelolithotomy. It was noted that the pelvis was intrarenal and a watertight closure was almost impossible. In order to prevent prolonged leakage and possible secondary obstruction, a double-J catheter was inserted. The patient made an uneventful recovery. Since post-operative IVU revealed an almost normal right kidney with tiny residual fragments, it was decided to remove the catheter. During cystoscopic removal it was noted that a portion of the double-J catheter remained in the ureter and renal pelvis. Antibiotics were prescribed and the patient was discharged, in the hope that spontaneous passage would occur.

One month later he was readmitted for removal of the catheter, which had remained in place. Under general anaesthesia, cystoscopy was performed and a Dormia stone basket was inserted into the right ureteric orifice. Under fluoroscopic guidance the fragment was engaged with the basket and removed (Fig.). He was discharged the following day with no complications.



Comment

If a fragment of a double-J stent remains *in situ*, it may be removed with the help of ureteroscopy or percutaneously (Le Roy *et al.*, 1986). Unfortunately, neither the equipment for percutaneous surgery and ureteroscopy nor the technical expertise is commonly available and open surgery may be the only solution. When ureteroscopy and percutaneous equipment are not available, removal of such fragments by the Dormia stone basket under fluoroscopic control is a safe and effective method (Grossman *et al.*, 1982) which should be tried before conventional surgical exploration.

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British Journal of Urology (1990), **66**, 109

Notices

C.-E. Alken Prize

An endowment fund has been established to further clinical work and research in the field of Urology by presenting an annual award of SwF 10,000 for outstanding scientific endeavours. The award will be for an unpublished work in the field of Urology. An award certificate will also be presented. The prize money may be divided among several contributors.

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Each submission must be affixed with a code word and must not bear the author's name. In addition, a sealed envelope labelled with the code word is to be included, containing on a separate sheet of paper the author's name and professional standing, together with the code word.

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The Prize consists of a fully sponsored visit to the American Urological Association Annual Five-day Meeting, together with a tour of Surgitek's manufacturing facility in Racine, Wisconsin. It is open to trainees in urology and consultants who are within 5 years of first appointment. Entrants should submit a written paper, which may be on any subject, but must be unpublished, and must not have been submitted previously for the Surgitek Prize, or other prizes. The winning entry will be the one which is considered to be "The most significant contribution to urology".

Entries will be judged by three members of BAUS Council nominated at the October meeting of Council. Papers should be submitted in triplicate to the Honorary Secretary by 1 January each year.

British Journal of Urology (1990), **66**, 110–112

Diary

1990

August 16–27	15th International Cancer Congress, Hamburg, FR Germany. Contact: Secretariat, Letzter Hasenpfad 61, D-6000 Frankfurt 70, Federal Republic of Germany.
August 22–24	Edinburgh Urological Festival. Contact; Urological Festival Secretary, Department of Surgery/Urology, Western General Hospital, Crewe Road, Edinburgh EH4 2XU.
August 29–September 2	8th World Congress on Endourology and ESWL. 6th Annual Research Symposium on ESWL. 5th Triennial Meeting of International Society of Urologic Endoscopy. Washington DC, USA. Contact: Arthur Smith, Dept. Urology, Long Island Jewish Medical Centre, 270–05 76th Avenue, New Hyde Park, New York 11042.
September 9–11	Biannual Conference of International Society for Dynamics of the Upper Urinary Tract. Stockholm, Sweden. Contact Anne-Charlotte Kinn, Department of Urology, St Görans Sjukhus, 112 81 Stockholm, Sweden.
September 9–11	International Uro-gynaecological Association Meeting, Uppsala, Sweden. Contact: Secretariat, Stockholm Convention Bureau, PO Box 6911, S-10239 Stockholm, Sweden.
September 9–12	Congresso Nazionale Della Societa Italiana Di Urologia, Ancona, Italy. Contact: OMNIA Meeting and Congressi s.r.l., Piazza San Bernardo 109, 00187, Roma. Tel: (06) 47 41 202–49 18 77.
September 12–15	20th Annual Meeting of the International Continence Society, Aarhus, Denmark. Contact Dr J. P. Norgaard, Institute of Clinical Experimental Research, University of Aarhus, DK–8000 Aarhus C, Denmark. Tel: 45 86 12 55 55 ext. 3364.
September 27–28	Fifth Annual Paediatric Urology Course, Cambridge. Places are limited and early application is advisable. Contact Mr R. H. Whitaker, Department of Urology, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ.
September 30–October 7	New York Section, American Urological Association Meeting, Budapest. Contact Eva Sloane, New York Section, American Urological Association, 2 East 103rd Street, New York, NY 10029, USA.
October 1–4	92nd Congress of French Urology. Paris. Contact Convergences, Eurochirurgie—A.F.C. 90, 120 Avenue Gambetta, 75020 Paris, France.
October 4–5	Urological Management of Spinal Injury. Institute of Urology, London. Contact Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 01 240 9115.
October 5–6	BAUS Autumn Meeting, City Hospital, Nottingham. Contact BAUS office.
October 11	Female Incontinence Update, Derby City Hospital. Contact: Mr C. P. Chilton, Derby City Hospital, Uttoxeter Road, Derby DE3 3NE.

October 16–19	25th Annual Meeting of the Egyptian Urological Association. Cairo, Egypt. Contact Dr Ahmad S. Bedair, 26 Adly Street, Flat 908, Cairo, Egypt.
October 17–19	Advanced Stone Management Course. Institute of Urology, London. Contact Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 01 240 9115.
October 17–19	25th Annual Meeting of the Egyptian Urological Association, Cairo. Contact: The Congress Secretary Ahmad Samy Bedair MD, 26 Adly Street, Flat 908, Cairo, Egypt.
October 25–26	Urological Management of Spinal Injury, Institute of Urology, London. Contact: Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115.
October 25–29	Second International Congress on "The Pelvic Floor"—Update Management. Fort de France, Martinique. Contact Bureau Congress: I.F.R.U.G. "The Pelvic Floor", 2 Square La Fontaine, 2, Paris 75016, France.
November 8–9	Renal Failure and Transplantation. Guy's Hospital, London. Contact Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 01 240 9115.
November 10	Basic Science and Urology Symposium, Glasgow. Contact Mr R Scott, Department of Urology, Royal Infirmary, 16 Alexandra Parade, Glasgow G31 2ER.
1991	
January 4	Final date for submission of abstracts for 1991 BAUS Annual Meeting.
January 22–25	Eighth Copenhagen Symposium on Endoscopic Urological Surgery. Herlev Hospital, Herlev, Denmark. Contact F. Rasmussen, Department of Urology, Herlev Hospital, 2730 Herlev, Denmark.
February 3–6	International Conference on Orgasm. New Delhi, India. Contact Professor Prakash Kothari, First International Conference on Orgasm, 203 A, Sukhsagar. N. S. Patkar Marg, Bombay 400 007, India.
February 23–March 2	Royal Society of Medicine, Section of Urology, Vail, Colorado. Contact: M. H. Ashken, Consulting Rooms, BUPA Hospital, Old Watton Road, Colney, Norwich NR4 7SZ.
June 2–6	American Urological Association, Metro Toronto Convention Centre, Toronto, Canada.
June 16–20	Canadian Urological Association Annual Meeting, Ottowa. Contact: Dr R. B. Auld, Suite 620, 5991 Spring Garden Road, Halifax, Nova Scotia, Canada B3H 1Y6.
June 25–28	BAUS Annual Meeting, Scottish Exhibition and Conference Centre, Glasgow. Contact: BAUS office.
September 1–6	6th World Congress in Ultrasound, Copenhagen. Contact: Spadile Congress Service, Sommervej 3, DK-3100 Hornbaek, Denmark. Tel: 45 2 20 24 96.

September 4–7	Twenty-first Congress of the International Continence Society. Budapest, Hungary. Contact A. Tankó, Üllői ut 78/b, Department of Urology, Semmelweis Medical School, H-1082 Budapest, Hungary. Tel: (36) 1 1139 016.

1992

January 10	Final date for submission of abstracts for the 1992 BAUS Annual Meeting.
May 10–14	American Urological Association, Washington Convention Centre, Grand Hyatt, Washington DC.
June 21–26	BAUS Annual Meeting, Bournemouth International Centre, Bournemouth. Contact: BAUS Office.
June 22–25	Canadian Urological Association Annual Meeting, Winnipeg. Contact: Dr R. B. Auld, Suite 620, 5991 Spring Garden Road, Halifax, Nova Scotia, Canada B3H 1Y6.
August 24–27	Third European Symposium on Uroradiology. Herlev, Denmark. Contact Dr H. S. Thomsen, Department of Diagnostic Radiology 54E2, Herlev Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark.

1993

May 16–20	American Urological Association, San Antonio Convention Centre, San Antonio, Texas.
June 13–17	Canadian Urological Association Annual Meeting, Toronto. Contact: Dr R. B. Auld, Suite 620, 5991 Spring, Garden Road, Halifax, Nova Scotia, Canada B3H 1Y6.

1994

May 15–19	American Urological Association, Moscone Centre, San Francisco, California.

Volume 66 No 2 August 1990

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REVIEW

Urinary Diversion

M. J. GLEESON and D. P. GRIFFITH

Scott Department of Urology, Baylor College of Medicine, Houston, USA

Permanent forms of urinary diversion are primarily applicable to patients with bladder cancer who require a cystectomy. An estimated 46,400 new cases of bladder cancer are diagnosed yearly in the USA; 25% of these patients will eventually require cystectomy and urinary diversion (Kline *et al.*, 1978; Silverberg and Lubera, 1988). Approximately 4000 additional urinary diversion procedures are undertaken yearly for benign vesical conditions (Barrett and Donovan, 1984). There is little doubt that having a cystectomy and some form of urinary diversion adversely affects the patients' lives (Jones *et al.*, 1980; Mansson *et al.*, 1988). Changes occur in mental and emotional attitudes, sexual relationships, ability to work and involvement in leisure activities (Mansson *et al.*, 1988).

Urinary diversion may be temporary or permanent. Temporary diversion by means of nephrostomy tubes is not recommended for long-term management. Permanent forms of urinary diversion require the development of either a continent (dry) or incontinent (wet) abdominal stoma or direct or indirect anastomosis of the ureters to abdominal or pelvic viscera. Permanent urinary diversion techniques are outlined in the Table.

Wet (incontinent) abdominal stomas

All require urinary collection devices.

Cutaneous pyelostomy. Cutaneous pyelostomy was originally described as a form of urinary diversion in children with tortuous dilated atonic ureters (Immergut *et al.*, 1969). The technique involves mobilisation of the renal pelvis through a subcostal flank incision. The pelvis is incised at a safe distance from the pelviureteric junction and is sutured to the posterior corner of the skin incision. The ease with which this can be performed in the child has been attributed to the paucity of the subcutaneous fat, the underdevelopment of the flank musculature and the relative mobility of the kidney. A later report of 68 procedures on 41 patients with an average follow-up of 32 months (range 1–86) described good overall results in 83% of patients, with improvement of impaired renal function in 71% and pyelographic improvement in 78% (Schmidt *et al.*, 1973). However, 13 early complications (skin irritation, wound infection, pyocystis, colon injury) and 18 late complications (skin irritation, appliance failure, stomal stenosis, calculus formation, mucosal prolapse) occurred. Although this technique was intended as a means of temporary diversion, long-term diversion for up to 80 months has been described. Diversion using this technique is usually incomplete, as most patients continue to pass small volumes of urine *per urethram*. Eventual operative stomal closure is relatively easy.

Cutaneous ureterostomy. The first elective cutaneous ureterostomy is usually credited to LeDentu in 1889. As a means of urinary diversion in children with dilated ureters or adults with advanced pelvic malignancy, this procedure became popular because of its simplicity, low mortality rate, applicability to both good and poor risk patients, freedom from electrolyte disturbances and easy accessibility of the urinary tracts for follow-up studies (Wasserman and Garrett, 1965). Its use, however, has many disadvantages, such as stomal stenosis, persistent chronic bacilluria, possible unsatisfactory drainage, calculus formation and the need to wear an external urinary collection device (Hendren, 1978). Eckstein and Kapila (1970) reported a 50% complication rate in their 62 patients, which included stomal gangrene, retraction or stenosis and urinary leakage. Attempts to prevent these complications have

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Table Urinary Diversion

Wet (incontinent) stomas	Cutaneous pyelostomy
	Cutaneous ureterostomy
	Ureterostomy *in situ*
	Jejunal conduit
	Ileal conduit
	Ileocaecal conduit
	Colonic conduit
Dry (continent) stomas	Gastric pouch
	Ileocaecal reservoir
Reconfigurated bowel	Ileal (Kock) reservoir
	Ileocaecal (Mainz) reservoir
	Caecoileal (Indiana) reservoir
	Penn pouch
	Colonic reservoir
Ureterosigmoidostomy	
Augmented and valved rectum	
Ureterogastrosigmoidostomy	
Rectal bladder	
Bladder substitutes	Ileum (Camey)
	Ileocolonic
	Sigmoid
Reconfigurated bowel	Ileum
	Ileocolonic pouch (Le Bag)
	Ileocaecal (Mainz) pouch
	Right colonic segment
	Rectosigmoid

included the use of external nylon splints, pedicle skin grafts, interposition of skin flaps using z-plasty techniques at the ureterocutaneous junction and loop and ring ureterostomies (Fish and Stevenson, 1949; Glenn and Alyea, 1960; Thompson and Ross, 1963; Perlmutter and Tank, 1968; Williams and Cromie, 1976). In selected cases it may be used with good effect as a means of temporary urinary diversion, but as a means of permanent diversion it should probably be reserved for the patient with advanced pelvic malignancy and limited life expectancy.

Ureterostomy in situ. The operative technique was outlined in detail by Walsh (1967). Through a gridiron incision the ureter is exposed extraperitoneally and a ureterotomy is performed to allow passage of a catheter proximally into the renal pelvis. Although use of this technique for long-term drainage was discouraged because of the risk of catheter encrustation, Walsh (1967) reported its use in 1 patient for 9 months (Campbell, 1954). He recommended using a catheter rather than a T-tube, because catheter changing was easy once a tract developed after 2 or 3 weeks.

Jejunal conduit. A jejunal conduit has been suggested as an alternative form of urinary diversion in cases where the ileum or colon cannot be used because of previous irradiation, surgery or concurrent disease. Originally, retroperitoneal placement of the jejunal loop was recommended to lower the incidence of intra-abdominal hernia (Clark, 1973). Its use is severely limited by the fact that 25 to 66% of patients develop a characteristic electrolyte imbalance known as jejunal conduit syndrome (Golimbu and Morales, 1973; Mansson and Lindstedt, 1978; Klein *et al.*, 1986). Clinically, the syndrome presents with anorexia, lethargy, nausea and vomiting. The electrolyte disturbances are hyponatraemia, hypochloraemia, hyperkalaemia, acidosis and azotaemia. As the urine enters the loop there is a shift of sodium chloride from the blood which is increased by the low urinary sodium concentration that often occurs in renal impairment. The resulting hypochloraemia and hyponatraemia diminish the extracellular fluid volume, including the intravascular compartment. Thus the plasma renal flow and the glomerular filtration rate are reduced. The reduction in glomerular filtration rate causes a reduction in renal sodium excretion which subsequently presents relatively hyponaturic urine to the jejunal mucosa, which attracts further large amounts of sodium from the extracellular fluid. Acidosis occurs because of a diminished hydrogen ion secretion in the kidney secondary to the hyponatraemia and the diminished glomerular filtration rate. This acidosis causes a potassium shift from the intracellular to the extracellular space. When the extracellular potassium level is high, a larger amount is excreted by the kidneys and subsequently more will be absorbed by the jejunal loop. The elevation of urea nitrogen is the result of decreased urinary urea excretion following the fall in glomerular filtration rate in addition to the high urea absorption by the conduit (Golimbu and Morales, 1973).

Electrolyte disturbances are more likely to occur if the jejunal segment is long, if the emptying of the segment is slow, if renal function is impaired and if the salt intake is low. Klein *et al.* (1986) recommended transperitoneal placement of the conduit to minimise its length and prophylactic oral electrolyte therapy to prevent electrolyte disturbances.

Ileal conduit. The first ureteroileal cutaneous urinary diversion was performed by Seiffert in 1935 and was later popularised by Bricker (1950). Although initially used in adults who required pelvic evisceration for cancer, its successful use in children was reported shortly thereafter (Bill *et al.*, 1954). The ureteroileal anastomoses may be performed individually (Bricker technique) or by first joining the ureters together before implantation, using a method which generally allows free ureteric reflux (Bricker, 1950; Wallace, 1970; Clark, 1979). The comparative use of the Bricker or Wallace anastomotic technique has been reported by Esho *et al.* (1974) to have little bearing on the later deterioration of the upper urinary tracts.

Sterile reflux alone does not lead to deterioration of renal function (Lenaghan *et al.*, 1972). However, animal studies have shown that in the presence of infection, 83% of kidneys anastomosed in a standard fashion to ileal conduits, as compared with 7% of kidneys anastomosed in an antireflux fashion to colon conduits, will develop histologically proven pyelonephritis (Richie *et al.*, 1974). A recent report of an antireflux ureteroileal reimplantation technique has confirmed the absence of reflux in 81% of cases studied by retrograde opacification after a minimum follow-up period of 3 years, and total renal function remained unchanged in all patients (LeDuc *et al.*, 1987).

Although the ileal conduit is considered to be the "gold standard" method of urinary diversion, it is not without complications. Long-term follow-up has shown that complications may occur in 80 to 85% of cases and include deterioration of the upper renal tracts, stomal problems, pyelonephritis, calculus formation, ureterointestinal stenosis and electrolyte abnormalities (Dunn *et al.*, 1979; Ashken, 1987; J. Urol., 1987).

Ileocaecal conduit. The use of an ileocaecal conduit for temporary and permanent diversion was described by Zinman and Libertino (1975). The ileocolic intestinal segment supplied by the ileocolic artery is used with ureteric anastomoses to the distal 10-cm segment of ileum. The ileocaecal valve is reinforced by plicating the caecum, using a technique similar to the Nissen (1956) fundoplication. Of 15 patients followed up for a maximum of 5 years, all had radiographically demonstrated competent ileocaecal valves at 40 to 60 mmHg injection pressure. Although the follow-up period was relatively short, no upper renal tract deterioration was seen.

The ileocolic intestinal segment is recommended because it has a constant blood supply, is rarely involved in compromising pathology such as diverticulitis, and its location allows easy creation of a stoma.

Colon conduit. This procedure was popularised by Turner-Warwick in 1960. Although the ease with which an antireflux ureterocolonic anastomosis can be performed is definitely advantageous, the conduit also functions differently from an ileal conduit (Mogg and Syme, 1969): it has less active peristalsis and in the absence of stomal stenosis the intraluminal pressure is lower.

In spite of this, with an average follow-up of 13.2 years, Elder *et al.* (1979) reported stomal stenosis in 61.5% of patients, ureterocolic stenosis in 22%, ureteric reflux in 58% and upper tract deterioration in 48.4%. Conduitography in another series demonstrated reflux in 13 of 24 renal units (52%), with follow-up to 5 years. This high incidence of reflux would seem to offset the benefit of using colon conduits, although it is generally considered that colon provides for a larger and more trouble-free cutaneous stoma. The use of the transverse colon as the conduit has been advocated in post-radiotherapy patients.

Dry (continent) abdominal stomas

All require intermittent self-catheterisation.

Gastric pouch. In 1956 Sinaiko reported his preliminary work in dogs using part of the fundus and body of the stomach to form a gastric pouch. A transcutaneous stoma was created using a brass cannula. Metabolic evaluation for up to 15 months showed few abnormalities and stimulated the author to apply this technique in humans. In 1960 he reported on the second such patient in whom he created a continent gastric reservoir with an abdominal stoma. However, the technique of continence creation was vague: "the abdomen was closed in layers around the pouch, much of which was in transit through the anterior abdominal wall in this obese patient." Follow-up for 4 months showed no metabolic abnormality, stable upper renal tracts radiographically and an asymptomatic *Proteus* urinary tract infection.

Ileocaecal reservoir. The ileocaecal reservoir was initially described by Verhoogen in 1908 but was rarely used until described in the American literature by Gilchrist *et al.* (1950). Continence depended on the natural ileocaecal valve, an antiperistaltic length of ileum and a small skin stoma. By this time, it had been shown that a 4–12 inch antiperistaltic segment of bowel allowed the creation of a non-leaking fistula (Mann and Bollman, 1931; Pearse, 1949). Gilchrist's operation also used a Coffey ureteric anastomosis to the caecum to prevent ureteric reflux. With follow-up for up to 20 years in 40 patients, Sullivan *et al.* (1973) reported a 94% continence rate, a 7% reflux rate and no deaths secondary to renal failure.

Many modifications for the creation of a stable continent valve have been described. In 1982, Benchekroun described the end-to-side ureteroileal anastomosis which used the natural ileocaecal valve to prevent reflux. A continent stoma was created by invaginating a 14-cm length of ileum on itself and anastomosing this between the open end of the ascending colon and the skin. This achieved continence in 24 of 27 patients and 12 patients had ureteric reflux.

Based on the early work by Kock (1969) and Zingg and Tscholl (1977), Mansson *et al.* (1984) and Webster and Bertram (1986) described the evolution of techniques to maintain continence using an intussuscepted ileocaecal valve. These modifications have included the diathermy of serosal surfaces, the use of silk sutures or staples, mesenteric debulking or exclusion, and the use of Marlex mesh or fascial slings around the base of the nipples.

Using a combination of techniques, Mansson and Colleen (1987) reported that 25 of 29 patients achieved continence, although 16 required revision of their reservoir outlets. The primary criticism of using a non-reconfigurated segment of bowel is that the amplitude of the pressure waves is high (>50 cm of water), although this diminishes with time (Mansson, 1984). This may lead to incontinence and although twice daily instillations of liquid diphenoxylate hydrochloride and atropine sulphate have been shown to decrease basal and contraction pressures as well as the frequency of spontaneous contractions, the use of non-reconfigurated bowel has largely been abandoned (Fowler *et al.*, 1987).

Ileal (Kock) reservoir. In 1969, Kock described the formation of a continent faecal reservoir from reconfigurated ileum in 5 patients. The concept of using reconfigurated bowel was based on Kock's earlier work in 1962, where reconfigurated ileum was used to form a bladder replacement which showed that augmentation inhibited the formation of peristaltic waves. The proven efficacy of clean intermittent self-catheterisation, together with the clinical application of the Kock pouch to urinary diversion, have stimulated interest in continent urinary diversion techniques (Lapides *et al.*, 1971, 1976; Kock *et al.*, 1978).

The Kock pouch is created from a 60 to 70 cm segment of ileum which is isolated on its vascular pedicle approximately 50 cm proximal to the ileocaecal valve. The middle part of this segment is detubularised and the proximal and distal ends of the bowel are invaginated into the reservoir to create nipple valves as described by Perl (1949). The nipple valves are stapled to the side of the reservoir and reinforced with a Marlex collar to prevent sliding and eversion. Kock *et al.* (1982) reported that malfunction of the nipple valves required surgical correction in 8 of their 12 patients, but continence was ultimately achieved in all cases.

Skinner *et al.* (1987) reported the results on 250 patients; 16% had early complications, with an operative mortality rate of 2% and a late complication rate of 31%. Most late complications are related to the nipple valve, resulting in leakage, difficulty with catheterisation or parastomal hernia formation, and can be corrected surgically to achieve continence in 98.5% of patients. Reservoir volume is usually 500 to 1000 ml and the pouch pressure rarely exceeds 20 cm of water. Skinner no longer recommends a Marlex nipple collar because of the risk of fistula formation.

Ileocaecal (Mainz) reservoir. The Mainz pouch is a mixed detubularisation of the caecum, ascending colon and 2 loops of ileum, and has been used since 1983 (Thuroff *et al.*, 1986). The ureters are implanted into the ascending colon using a tunnelled antirefluxing technique and continence is achieved by an ileoileal intussusception nipple technique.

The original publication of this technique in 23 patients reported that 11 had bladder augmentation and 12 had urinary diversion to cutaneous stomas. With a mean follow-up of 4.8 months, there were 3 major complications and no operative mortality. Of the 12 patients with cutaneous stomas, all patients with ileoileal intussusception valves were continent, as were 3 of 4 patients with alloplastic stomal prostheses.

The Mainz experience has been updated to include 100 patients, 34 of whom had bladder augmentation, 15 had total bladder substitution after cystoprostatectomy and 51 had continent urinary diversion (Thuroff *et al.*, 1988). With a mean follow-up of 23 months, peri-operative complications occurred in 7 patients and late complications in 18. Most of the late complications were related to the continent nipple. In 4 patients a prosthetic stoma was inserted but in each case this had to be removed because of chronic infection. Sutured intussuscepted nipples tended to fail with time and were revised with staples in 7 cases which included stapling the nipple valve to the side wall of the reservoir. The mean capacity in continent diversion patients was 622 ml, with pressures ranging from 33 cm H_2O (50% capacity) to 41 cm H_2O (100% capacity).

Caecoileal (Indiana) reservoir. The Indiana reservoir was developed in 1982 and consists of approximately 20 cm of caecum and ascending colon whose tubular configuration is disrupted with an ileal or sigmoid patch, antireflux ureterocaecal anastomoses along the taenia and a continence mechanism based on the ileocaecal valve and plicated 12 to 15 cm of terminal ileum. In a series of 29 patients, 24 of whom had abdominal wall stomas, 24% had post-operative complications; 93% had acceptable daytime continence (2 patients had prosthetic sphincters inserted) and 76% nocturnal continence after a mean follow-up of 14 months (Rowland *et al.*, 1987).

Penn pouch. To date, only 1 patient has had a Penn pouch. The reservoir consists of an augmented ileocaecal pouch in which the appendix is removed but maintained on its vascular pedicle. The tip of the isolated appendix is implanted into the caecum and the caecal end is brought to the skin as a small catheterisable stoma using the Mitrofanoff principle (Mitrofanoff, 1980; Duckett and Snyder, 1987).

Colonic reservoir. Lockhart *et al.* (1988) presented their experience with a reservoir fashioned by detubularising and anastomosing the ascending and proximal transverse colon, with tunnelled antireflux ureterocolonic anastomoses and a plicated terminal ileum to achieve a continent stoma in 20 of 21 patients. One of their patients developed post-operative intestinal obstruction and 2 ureteric anastomoses required percutaneous dilatation.

Ureterosigmoidostomy. Until the 1960s, ureterosigmoidostomy, which was initially described by Lloyd (1851), was a popular form of urinary diversion. Realisation of the importance of preventing faecal reflux resulted in a gradual evolution of ureterosigmoid anastomotic techniques, from the muscularising technique of Stiles (1911) and the tunnelling technique of Coffey (1911) to the direct mucosa-to-mucosa anastomosis of Nesbit (1949), the combined tunnel and mucosa-to-mucosa technique of Leadbetter (1951) and the nipple creation of Mathisen (1953). Ureterosigmoidostomy should be considered only in patients with normal renal function and normal ureters in whom rectal fluid continence has been demonstrated.

The long-term complications of ureterosigmoidostomy include pyelonephritis, renal calculi, loss of renal function, hyperchloraemic acidosis, colonic carcinoma and faecal incontinence. Pyelonephritis is generally related to the presence of reflux and can be reduced by the combined tunnel and mucosa-to-mucosa anastomotic technique (Clarke and Leadbetter, 1955). Renal calculi which develop in patients after all forms of urinary diversion are related to urinary infection with urease-producing bacteria and stasis. Hyperchloraemic acidosis and hypokalaemia present as thirst, lethargy, anorexia, nausea, vomiting, diarrhoea and coma. Electrolyte abnormalities occur in up to 80% of cases (*J. Urol.*, 1987).

The risk of developing colon cancer after ureterosigmoidostomy is between 5 and 11%, with a further 17% of patients having colonic adenomas (Stewart *et al.*, 1982; Zabbo and Kay, 1986). This represents a relative risk 150 times greater than that of the normal population. The aetiology has been postulated to be the carcinogenic action of one of the N-nitrosamines which result from the interaction of urinary nitrates and endogenous secondary amines in the presence of a mixed bacterial flora (Stewart *et al.*, 1981). Carcinomas usually develop after a latency period of more than 15 years and may be preceded by an adenoma (Stewart *et al.*, 1982; Zabbo and Kay, 1986). Since carcinomas are usually situated at or near the ureteric anastomotic site, any changing hydronephrosis should be carefully evaluated.

In general, 10 years after the patient has had a ureterosigmoidostomy, flexible sigmoidoscopy should be performed at least yearly and perhaps every 6 months. Should the patient subsequently have an alternative form of urinary diversion, the distal ureter with a surrounding cuff of colonic tissue should be excised. Although liquid faecal incontinence is usually avoided if rectal continence to fluid is confirmed prior to surgery, McFarlane *et al.* (1979) reported that every patient in a series of 9 children had some degree of incontinence.

Augmented and valved rectum. A new urinary diversion technique which involves the fashioning of an antireflux valve at the rectosigmoid junction and augmentation of the rectum with an ileal patch has been described by Kock *et al.* (1988). The ureteric anastomoses may (a) be incorporated into the rectosigmoid valve, (b) be implanted into the rectum using a standard submucosal tunnel technique or (c) be anastomosed to a second antireflux valve created in the detubularised ileal augmentation. The operative procedure is protected by a covering transverse colostomy for 6 to 8 weeks. All 16 patients followed up for 3 to 14 months were completely continent, with a nocturnal frequency of 0 to 2. The upper renal tracts deteriorated radiographically in 1 patient and 3 had reflux of rectal contents into the sigmoid. Reflux into 1 ureter was also seen. Although this procedure was developed to minimise the risk of metabolic disturbance, as occurs after a ureterosigmoidostomy, the significant risk of carcinoma persists and it should be used with caution in patients with a life expectancy of 15 years or more. Long-term follow-up of the new ureteric anastomosis technique is necessary to determine its efficacy.

Ureterogastrosigmoidostomy. In 1969, Karow and Thompson performed ureterogastrosigmoidostomy on 5 dogs using a segment from the middle third of the greater curvature of the stomach. Their working hypothesis was that a hydrochloric acid-secreting pouch of stomach would prevent ascending pyelonephritis and also protect against hyperchloraemic acidosis. Although Hypaque enemas confirmed the absence of ureteric reflux and serum electrolytes remained normal in all cases for 6 to 7 months, urinary tract infections occurred in all cases and 4 of 5 kidneys showed microscopic evidence of pyelonephritis. This technique has not been applied clinically.

Rectal bladder. The use of a rectal bladder was developed by Heitz-Boyer-Hovelacque in 1912. In the last 20 years, the operation has generally been used in children with bladder exstrophy (Bracci, 1968; Tacciuolli *et al.*, 1977). The procedure involves transection of the bowel at the rectosigmoid junction with closure of the open end of the rectum. The ureters are anastomosed over stents to the rectum. An incision is made at the posterior mucocutaneous margin of the anus and an intersphincteric plane is developed to allow the pull-through of the sigmoid colon, which is sutured to the anal mucosa anteriorly and the skin posteriorly.

This operation is more applicable to children than to adults because of the elasticity of their tissues, the length and softness of the mesocolon and the shorter pelvis (Bracci, 1968). Tacciuolli *et al.* (1977) reported continence in 20 of 21 patients after a follow-up of 1 to 16 years; 3 patients developed uretero-rectal strictures but all were successfully repaired. It was recommended that surgery should be performed in the first 18 months of life, when a baby is still unable to discriminate the stimulus to defaecate, or should be delayed until the child is at least 4 years old so that the adequacy of the anal sphincter can be assessed and so that the patient will be better able to distinguish between the stimuli for micturition and defaecation.

Bladder substitutes

These are bowel segments which store urine and empty either by spontaneous micturition or by intermittent transurethral catheterisation (Fowler, 1987).

Ileal bladder. Tizzoni and Foggi (1888) were the first to attempt the construction of a functional bladder substitute using ileum. In 1979, Camey and LeDuc reported their experience with the Camey procedure and more recently they reported their results since 1959 (Lilien and Camey, 1984). The procedure involves isolation of a 40-cm segment of ileum which is brought into the pelvis to enable a mucosa-to-mucosa anastomosis to be performed between the membranous urethra and the midpoint of the U-shaped ileal loop at its antimesenteric border. Antireflux ureteric implantation is achieved using an original technique of placing the distal ureter in a 3-cm mucosal sulcus which is created by incising the mucosa (LeDuc *et al.*, 1987). It has been shown that the mucosa will grow over the distal ureter to form a submucosal tunnel. In a study of 84 patients using 2 surgical teams (1 for cystectomy and 1 for enteroplasty), the average operative time was 9 h and there were 4 deaths, most of which occurred early in the series (Lilien and Camey, 1984). Daytime continence was achieved in 90% of cases; nocturnal continence depended on whether the patients were willing to get up to void every 2 to 3 h and has since been reported to be 50% (Allen *et al.*, 1985). Ureteric anastomosis resulted in stenosis in 1.5% and successful prevention of reflux in 85% (LeDuc *et al.*, 1987). Further reports on the use of this technique in the USA have produced similar antireflux results, with daytime continence in 20 to 78% of patients and enuresis in 20 to 100%. Bladder capacity ranged from 120 to 500 ml, with residual volumes up to 120 ml and bladder pressures up to 100 cm of water produced by contractions (Fowler, 1987; Goldwasser *et al.*, 1987; Roehborn *et al.*, 1987).

Ileocolonic bladder. The use of an ileocaecal bladder was initially reported by Gil-Vernet in 1956 and later in 1965. The operation required isolation of 23 to 30 cm of distal ileum together with the caecum and the ascending colon. The ureters were anastomosed end-to-side to the ileum and an end-to-end or side-to-end caeco-urethral anastomosis was performed. Of his 26 patients, 1 died post-operatively of peritonitis, 1 had a prolonged paralytic ileus and 1 developed a bladder neck contracture. Ureteric reflux, which usually occurred, was said to disappear with time and did not usually result in pyelonephritis. No mention was made of the incidence of incontinence. Alcini *et al.* (1988) reported daytime continence in a series of 30 patients and enuresis, which was present in all cases, tended to improve over a 2-year period.

Sigmoid bladder. The sigmoid bladder substitute is usually performed in a similar way to the Camey procedure with a side-to-end colo-urethral anastomosis. Its advantage over an ileal segment is that it has a larger capacity and lower enuretic rate despite higher reservoir pressures (Hradec, 1965). Hradec reported that 60 of 76 patients with bladder tumours had cystectomy and sigmoid bladder substitution with a 6.5% mortality rate. He stated that continence following total cystectomy is secured by the external sphincter alone, which is usually relaxed during sleep and thus results in enuresis.

Ileal reservoir. There have been many reports of different ways to detubularise ileum to form a reservoir which can be anastomosed to the urethral stump. Abu Farha *et al.* (1986) anastomosed a standard Kock pouch to the urethra to achieve continence in 6 of 8 patients. Tscholl *et al.* (1987) created an ileal S-pouch in 7 patients. Ureteric reflux was prevented by an intussuscepted nipple where the afferent limb entered the pouch. Five patients, including 1 female, had complete continence and 2 had some daytime stress incontinence with normal nocturnal continence. Pouch capacities ranged from 200 to 450 ml with residual volumes less than 100 ml. Weidner *et al.* (1988), Studer *et al.* (1988) and Melchior *et al.* (1988) described reconfigurated U-shaped ileal bladders with varying techniques to prevent ureteric reflux at the uretero-afferent limb anastomoses. Weidner *et al.* (1988) reported daytime continence in all 4 patients but 1 female had enuresis. Pouch capacity was 300 to 400 ml in all patients with residual volumes less than 50 ml and contraction amplitude less than 40 m bar. All 13 patients reported by Studer *et al.* (1988) were continent, with a diurnal frequency up to 7 times and nocturia up to 3 times. Pouch pressures varied from 5 to 35 cm H_2O with no residual urine exceeding 20 ml. Melchior *et al.* (1988) presented their results in 44 patients with follow-up to 20 months. Bladder capacity increased, residual volume decreased and continence rate increased gradually with prolonged follow-up. Of 7 patients followed up for more than 9 months, bladder capacity ranged from 300 to 700 ml, residual volume was less than 50 ml and intravesical pressure was less than 21 cm of water. All patients had day-time continence but only one-third were continent at night. Hautman *et al.* (1988) described detubularising a U loop of ileum to form a reservoir with direct uretero-reservoir anastomoses using the LeDuc-Camey technique. They achieved complete continence in 8 of 11 patients and 3 patients had stress incontinence. Bladder capacities were up to 530 ml with residual volumes less than 50 ml and reservoir pressures less than 40 cm of water at 100% capacity.

Ileocolonic pouch (Le Bag). The use of Le Bag was described in 10 patients by Light and Engelman (1986). This procedure involves division of the terminal ileum (20 cm) and ascending colon along their antimesenteric borders and anastomosing the open loops of bowel together to form a pouch. The ureters are anastomosed to the colonic portion of the pouch using a submucosal tunnel technique and an end-to-end urethro-ileal anastomosis is performed. Pouch capacities range from 400 to 700 ml with pressures of 20 to 45 cm of water. Continence depends on the inherent function of the residual sphincteric mechanism. A recent update on 11 patients after a mean follow-up of 2 years found that all patients were continent (required less than 3 pads per day), with 50% requiring the artificial urinary sphincter to reach this state (Marks *et al.*, 1988).

Ileocaecal (Mainz) bladder substitute. Fifteen cases of total bladder substitution using a Mainz pouch anastomosed to the urethra have been reported (Thuroff *et al.*, 1988). In 2 of these cases the urethra was anastomosed to the appendiceal stump. Fourteen patients had daytime continence and 1 had stress incontinence. Eleven were continent at night and 4 required a condom urinal. Mean bladder capacity was 510 ml, with pressures ranging from 33 cm H_2O (50% capacity) to 41 cm H_2O (100% capacity).

Right colonic segment. In 1986, Goldwasser *et al.* described partial detubularisation of the right colon with ureteric anastomoses using a submucosal tunnelling technique or the LeDuc-Camey technique and urethral anastomosis to the caecum.

They achieved continence in 3 male patients. Cystometric evaluation on 1 patient showed contractions of 20 cm of water at 220 ml capacity and 44 cm of water at 320 ml capacity. As follow-up was only 2 months, it remains to be seen if this technique of partial detubularisation of a segment of bowel is as effective as total detubularisation.

Rectosigmoid. In 1970, Ong reported using a detubularised rectosigmoid segment of bowel to achieve continence in 13 of 21 patients studied after cystectomy for bladder carcinoma. Although not specified, it is likely that all patients were male. Bladder capacities ranged between 200 and 500 ml with pouch pressures of 18 to 60 mm Hg.

Summary

Although the ileal conduit must be regarded as the "gold standard" technique of urinary diversion, many long-term complications result and patients must wear urinary collection devices with their associated psychological and social limitations. The recent interest in continent diversions was primarily an attempt to improve the quality of life rather than improve survival or reduce renal and metabolic complications. Although continent stomas can be achieved with low pressure reservoirs fashioned from detubularised or augmented bowel, many operations may be required to perfect the continent stoma. Long-term results using continent reservoirs are awaited. It seems that a bladder substitute using reconfigurated bowel is preferable to a continent reservoir but continence remains a problem and all of the techniques lack long-term follow-up.

The use of bladder substitutes in females is limited by the need to use a prosthetic sphincter to achieve continence.

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The Authors

M. J. Gleeson, MCh, FRCSI, Post-doctorate Fellow in Urology
D. P Griffith, MD, FACS, Professor of Urology.

Requests for reprints to: M. J. Gleeson, c/o Department of Urology, St James's Hospital, P.O Box 580, Dublin 8, Ireland.

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What on Earth are we Drinking?

P. D. MAYNE and L. EDWARDS

Departments of Chemical Pathology and Urology, Westminster Hospital, London

Summary—During the past few years there has been a considerable increase in the number and variety of still and carbonated bottled drinking waters, which have an enormous variation in calcium content ranging from 0 to over 500 mg/l.

Patients with upper urinary tract stones are often advised to maintain a high fluid intake in order to achieve an increased urinary output. If they find tap water unpalatable and drink bottled water instead, they could significantly increase their daily calcium intake by as much as 1.5 g. The majority of bottled waters presently available in this country, together with tap water samples from throughout the British Isles, have been analysed and the results suggest that there are some waters which stone formers should avoid.

The last few years have seen an enormous increase in the variety and popularity of bottled drinking waters, both still and carbonated. There are several reasons why people buy bottled water. These include the public concern that tap water might be contaminated with organic and inorganic chemicals, such as aluminium, lead, pesticides and nitrates (Which?, 1989). In some areas there has been a loss of taste for tap water. Publicity campaigns and advertising by bottled water companies have led to a greater awareness by the general public of their availability and the advertising campaigns often give the impression that bottled waters are pure, free of contamination and beneficial for health. The mineral content of bottled water is often shown on the labels and there is an enormous variation in this advertised content.

The aim of management of patients with renal stones and idiopathic hypercalciuria is to decrease urinary calcium excretion and to increase urinary volume. If patients find tap water unpalatable and drink bottled water instead, they could significantly increase their daily urinary calcium excretion. We have analysed many of the bottled waters available in this country, together with tap water samples from throughout the British Isles.

Materials and Methods

Water samples were collected from as many kitchen tap water supplies as possible. Collectors were asked to make sure that the water came from the rising main and to flush the tap for half a minute before collecting the samples. Samples from faraway places were sent by post in plastic universal containers. Water from wells was collected by this same method. Commercial bottled waters were, in the main, purchased by us in and around London and these were also tasted for palatability.

We assessed the effectiveness of a "Brita, fill and pour" water filter jug in removing calcium from London tap water. The Brita was filled 3 times/day with approximately 1.75 l of tap water per fill. The calcium content of the tap water and filtrate was assayed at regular intervals for up to 14 weeks after a new filter had been fitted.

The samples were analysed by standard laboratory techniques for both calcium concentration and pH. Calcium hardness was defined as water with a calcium concentration >50 mg/l (personal communication, Thames Water Authority). Costings were recorded at the time of purchase and, in the case of foreign waters, an appropriate currency conversion factor was applied.

Based on a Poster Demonstration at the 45th Annual Meeting of the British Association of Urological Surgeons in St Helier, June 1989

Results

In all, 122 samples were analysed. Of these, 69 were tap water samples from throughout the British Isles, 6 came from holy wells or spas and 47 were bottled water samples from throughout Europe. The sources are indicated in Tables 1 to 3. No distinction was made between still and carbonated water. Indeed, all of the waters tested were carbonated except one.

Table 1 Calcium Concentration of Tap Water from the British Isles

Source	*Origin*	*Calcium (mg/l)*	*pH*
Borrowdale	England	0.8	6.0
Dumbarton	Scotland	1.2	7.2
Preston	England	2.8	8.3
Dolgellau	Wales	4.0	7.4
Dublin	Rep Ireland	8.8	7.1
Llanbrynmair	Wales	12.8	7.5
Bradford	England	15.2	7.0
Llanelli	Wales	15.6	7.6
Newbridge-on-Wye	Wales	30.0	7.6
Llandovery	Wales	36.0	7.7
Acton Burnsall	England	36.2	7.4
Aberdeen	Scotland	37.2	8.0
Newcastle	England	40.0	7.0
Brecon	Wales	43.2	7.3
Galway	Ireland	47.6	7.0
Walsall	England	62.0	8.1
Alderney	Alderney	67.0	7.2
Bristol	England	82.0	7.2
Southampton	England	82.8	7.3
Swindon	England	84.0	8.1
Treffynnon	Wales	93.7	7.5
Greater London (S)	England	96.0	7.9
Bournemouth	England	96.0	7.5
Loughrea	Ireland	96.4	7.2
Milton Keynes	England	102.0	6.7
London (south)	England	102.8	7.7
Marlborough	England	108.0	7.8
London (north)	England	108.0	7.8
Farnborough	England	114.0	7.7
Greater London (N)	England	121.2	7.6

Table 2 Calcium Concentration of Water from Wells and Spas

Source	*Origin*	*Calcium (mg/l)*	*pH*
Lourdes	France	42.4	7.9
Abbeywell	England	53.2	7.0
Knock	Ireland	72.8	7.9
Bath Spa	England	79.2	7.0
Our Lady's	Ireland	102.4	7.6
St Winefrede's	Wales	119.6	7.3

Table 3 Calcium Concentration and Cost of some Bottled Water from Europe but Available in the UK

Name	*Origin*	*Calcium (mg/l)*	*pH*	*Price (pence/l)*
Ramlosa	Sweden	n.d.	5.9	79
Caramulo	Portugal	0.8	7.2	96
Sousas	Spain	1.6	8.0	56
Mont Claire	France	2.4	8.4	47
Divona	France	4.0	7.0	30
Decantae	Wales	6.0	7.9	46
Lifestyle	Wales	7.6	4.5	27
Volvic	France	8.4	7.7	25
Fiuggi	Italy	11.6	7.5	48
Aqua Pura	England	13.2	5.1	29
Bruisead	Holland	13.6	5.4	46
Spa	Belgium	17.2	6.7	23
Braevisge Spring	Scotland	17.2	9.0	36
Caledonian	Scotland	17.2	9.0	36
Connemara	Ireland	19.6	7.5	35
Ma'ayanot	Israel	22.0	7.5	n.a.
Eden	Israel	24.0	7.6	n.a.
Glendale	Scotland	28.0	7.4	36
St Yorré	France	29.2	6.6	48
Highland Spring	Scotland	32.4	7.8	34
Malvern	England	32.4	6.8	35
Brecon	Wales	44.0	7.4	42
Evian	France	46.8	8.3	28
Buxton	England	54.0	5.4	25
Moderanno Fonte	Italy	61.2	5.5	73
Ballygowan	Ireland	64.4	7.8	42
Strathmore	Scotland	68.0	7.5	42
Monastere	Belgium	73.6	6.8	46
Beckerich	Luxemburg	92.0	7.7	30
Dorset	England	92.8	7.4	39
Ashbourne	England	95.2	7.5	39
Chiltern Hills	England	98.8	5.6	33
Vitelloise	France	98.8	5.4	58
Madonna d'M	Italy	103.6	5.8	57
Apollinaris	W Germany	104.4	6.9	47
Preblaues	Spain	115.2	6.7	54
Glenpatrick	Ireland	118.8	7.6	46
Smita Morjarra	Spain	126.8	6.7	n.a.
Perrier	France	149.6	6.6	55
Ferarelle	Italy	152.4	6.9	68
Vittel	France	195.0	7.6	65
San Pellegrino	Italy	205.2	5.5	82
Badoit	France	205.6	6.9	42
Alpquelle	Austria	230.0	5.9	62
Sangemini	Italy	328.4	6.6	74
Contrex	France	468.0	6.4	42
Crodo	Italy	513.6	5.0	60

English tap waters were generally hard, with London and the south-east being the hardest. The further north the sample, the softer the water became. Borrowdale, in the Lake District, provided the softest water sample of all those tested. Welsh and Scottish waters were uniformly soft, while those from the Republic of Ireland were mixed.

There was a wide variation in the hardness of bottled waters. Ramlosa water (Helsingborg, Sweden) contained no detectable calcium, while Crodo (Milan, Italy) was the hardest of all samples analysed. Italian waters were, in general, very hard. French waters showed a wide distribution in calcium content, from the very soft (Mont Claire at 2.4 mg/l) to the very hard (Contrex at 460 mg/l). English bottled waters showed a fair scatter but the hardest (Chiltern Hills, with a calcium content of 98.8 mg/l) was softer than most London tap waters.

The cost of bottled waters in pence/l also showed a wide scatter. Spa was the cheapest at 23p. Many imported bottled waters were cheaper than those from the British Isles (Table 3).

Although taste must be entirely personal and subjective, for us Crodo tasted best of all; its sharp freshness may have been related to its apparent acidity—it had the lowest pH of all samples tested. Aqua Pura, Brecon, Contrex, Ramlosa, Decantae, Malvern, Spa and Perrier all performed well. Only the carbonated versions of bottled waters were tested.

The effectiveness of the Brita filter jug was also assessed. It worked very well, removing 66% of the filtered calcium at the beginning of its filter life. The calcium content of the filtrate then rose, so that by 8 weeks the filter had completely lost its effectiveness. Thereafter, the calcium content of filtered water increased (Fig.).

Many bottled waters had labels indicating their mineral content. Most manufacturers' analyses were correct within 10% when compared with the results of our analyses (Table 4).

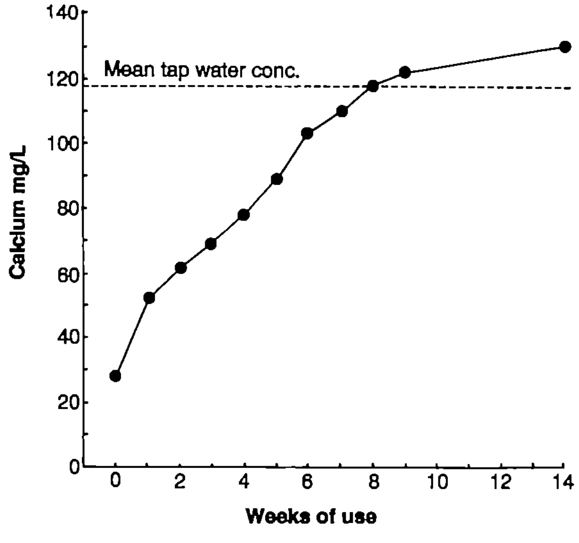

Fig. Changes in filtrate calcium concentration with time, using a "Brita, fill and pour" water filter jug

Table 4 Difference between the Advertised and Measured Calcium Concentration of some Bottled Waters

	Calcium		
	Advertised (mg/l)	*Measured (mg/l)*	*Error (%)*
Within 10%			
Brecon	47 5	44.0	+1.1
Ballygowan	60 0	64.4	−7.5
Beckerich	91 2	92 0	−1.1
Ashbourne	102 0	95.2	+7.1
Glenpatrick	110 0	118 8	−0.8
Vittel	202 0	195 6	+3.3
San Pellegrino	212 0	205 2	+3 3
Sangemini	343.5	328 4	+4 6
Contrex	451 0	468 0	−1 0
Crodo	520 0	513 6	+1.2
Harder than advertised by more than 10%			
Moderanno Fonte	50 0	61 2	22
Softer than advertised by more than 10%			
Ma'ayanot	29 0	22.0	24
Badoit	272 0	205.6	24
Eden	35 7	24.0	33
Evian	78 0	46.8	40
Highland Spring	55 0	32.4	41

Discussion

Urinary calcium excretion is just one of a number of risk factors associated with the formation of calcium oxalate or phosphate stones (Robertson and Peacock, 1980). More important is the urinary oxalate excretion and urine volume, although the significance of the latter is debated (Robertson *et al.*, 1978). In patients with renal stones and idiopathic hypercalciuria, a lower urinary calcium excretion is associated with reduced stone activity (Marickar and Rose, 1985); there is no significant correlation between total water hardness and the incidence of renal stone formation (Shuster *et al.*, 1982; Power *et al.*, 1987). It is generally accepted that, in the management of urolithiasis, it is desirable to reduce dietary oxalate intake, to reduce urinary calcium excretion and increase the daily urinary volume (Rose, 1986). Patients are frequently advised to drink about 3 litres of fluid/day.

This study was undertaken to determine the calcium concentration in drinking tap water and bottled waters which are generally available within the UK, in order to identify whether there were some waters which should be avoided in the management of idiopathic hypercalciuric stone formers. Increased public awareness of reported incidences of contamination of drinking tap water and the adverse media publicity have contributed to the increase in sales of bottled water (Road, 1989). It was estimated that during the summer of 1989, sales of bottled water increased by 81%, with a projected annual market value in the UK in excess of £200 million (Harris, 1989). The media publicity surrounding the European court's decision to prosecute the UK because of the quality of drinking water in certain areas will undoubtedly assist the sales of bottled water.

Our results regarding the calcium content of drinking tap water are in broad agreement with those published by the British Regional Heart Study (Pocock *et al*., 1980). However, of the 44 bottled waters analysed, 50% could be described as moderately hard and 12% were harder than the hardest tap water from within the British Isles. Crodo has a calcium content of 513.6 mg/l, in comparison to semi-skimmed milk, which has a calcium concentration of about 1300 mg/l. The average cost of a litre of mineral water was 46p (range 23–96); processing contributes approximately 7% to the overall costs/l (Erlichman, 1988).

The calcium content of bottled waters from the British Isles did not always correspond to the level of hardness of the local tap water. Brecon Spring Water, with a calcium content of 44 mg/l, comes from near Llandeilo, where the local tap water had a calcium content of 25.6 mg/l. Connemara and Galway are within 30 miles of each other, yet the calcium content of their respective waters differed by 28 mg/l. Connemara is situated in a pre-Cambrian area, which accounts for its softness. Galway is situated in an area of basic igneous rock formation which does not contain calcium, but is adjacent to the large mass of carboniferous limestone which makes up most of the body of the island. These results suggest that the Galway water supply comes from a source to the east of the city. Buxton derives its water supply from the same kind of limestone and Ashbourne from Keuper Marl, both waters being hard.

In hard water areas, the Brita filter can reduce the calcium content by up to 66%. However, a filter change every 200 litres of filtered volume is recommended if a satisfactory degree of water softening is to be accomplished. Failure to do so may actually increase the calcium content of the filtered water. Other filter units are available and appear to be equally effective.

This study confirms that there is a wide range in the calcium content of drinking tap water from throughout the British Isles. However, with the importation of a large number of bottled waters the range has increased considerably and there are now some waters that, we believe, patients with renal stones and hypercalciuria should avoid.

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The Authors

P. D. Mayne, MSc, FRCPI, MRCPath, Senior Lecturer, Department of Chemical Pathology.

L. Edwards, MA, MChir, FRCS, Consultant Urologist.

Requests for reprints to: L. Edwards, Department of Urology, Westminster Hospital, Page Street, London SW1P 2AR.

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Ultrasonic Imaging for Extracorporeal Shockwave Lithotripsy: Analysis of Factors in Successful Treatment

E. A. KIELY, D. MADIGAN, P. C. RYAN and M. R. BUTLER

Department of Urology, Meath Hospital, Dublin, Ireland

Summary—The emergence of real-time ultrasonic imaging for extracorporeal shockwave lithotripsy poses questions regarding the factors and techniques which facilitate stone imaging for clinicians with no previous practical experience in ultrasonography. The ability of these clinicans to assess when stone disintegration has been achieved also needs to be confirmed. A wide range of data was recorded from each of 2688 lithotripsy treatments performed over a 2-year period using the EDAP LT.01 ultrasound-imaged piezoelectric lithotriptor. An analysis of these data was performed using a comprehensive microcomputer-based statistics package.

The mean time taken for stone imaging and positioning was reduced from 11.2 to 7.5 min over the 2-year period. Obese patients and those with renal pelvic stones were best imaged in a lateral position. Overall there was no difference in percentage stone disintegration or clearance between treatments in the supine or lateral positions, but a significant reduction in the clearance of small caliceal stones resulted when the lateral position was used.

Factors associated with a significantly greater percentage of stone disintegration and clearance included pain experienced by the patient during fine adjustment of the processing head during treatment, acoustic focus attenuation and widening and acoustic shadow widening as detected by the urologist at the end of treatment.

Among the factors not associated with significant alterations in the percentage of stone disintegration or clearance were the lithotriptor operator, the side or site of the calculus, obesity and shockwave frequency or power.

This study confirmed the ability of urologists to develop expertise in ultrasonography for renal stone imaging and to interpret successfully the subtle signs of stone disintegration.

The success of extracorporeal shockwave lithotripsy (ESWL) in treating urinary tract calculi has led to its widespread use in clinical urology. Among the variations introduced in the second generation lithotriptors were continuous real-time ultrasound imaging and piezoelectric shockwave generation. The results of treatment with various lithotriptors have shown few differences apart from the superiority of fluoroscopy in imaging ureteric stones and the improved tolerance by patients of piezoelectric shockwave lithotripsy (PSWL) (Marberger *et al.*, 1988; Kiely *et al.*, 1989).

Fluoroscopy has an obvious initial appeal for the urologist, who is familiar with X-ray imaging in everyday practice and who usually has no practical experience in ultrasonography. However, ultrasonography (already mastered by gynaecologists) is used increasingly in routine clinical urology (Thüroff and Becht, 1988). In the present study, patients with urinary calculi were treated using the EDAP LT.01 piezoelectric lithotriptor which employs ultrasound for calculus imaging and monitoring. It also allows ultrasound images to be stored as treatment progresses, thus enabling precise com-

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parison of stone images. An ultrasound stone image is characteristically a linear bright focus with an acoustic shadow distally. The supine position is standard for patient imaging and treatment. When the clarity of the renal stone image is poor, however, it is improved by placing the patient in the full lateral position. During successful treatment the acoustic focus becomes attenuated and widened, as does the acoustic shadow. In addition to avoiding radiation exposure, therefore, ultrasonography allows the effect of treatment to be monitored continuously, so that lithotripsy can be used more accurately and with greater cost-efficiency. The changes in ultrasound image can be subtle, however, and we have assessed the ability of urologists to interpret them.

The shockwave focus of the EDAP LT.01 is 5 mm wide and 15 mm high (Colman and Saunders, 1989). The centre of this area is represented on the ultrasound monitor by the point of a V-shaped cursor. The frequency and power of the shockwaves can be varied greatly, but as these factors increase so too does patient discomfort. Therefore 2.5 Hz is the standard shockwave frequency used, since most patients tolerate 100% power at this frequency. Where discomfort is unacceptable, even on reducing power toward 50%, the shockwave frequency is reduced to the minimum rate of 1.25 Hz. On activating the shockwave generator a short sharp sound is produced which coincides with each shock. The pitch of this sound changes when the shockwaves are focused on and off the stone and this may help to confirm correct stone positioning, as may the occurrence of discomfort to the patient during this manoeuvre.

The ability of urologists to master ultrasonography was assessed in terms of the time taken for stone imaging over the study period; their interpretation of the ultrasonography signs of stone disintegration was checked radiologically. A further aim was to establish whether stone disintegration and clearance were related to the degree of sound change and the discomfort experienced by the patient when focusing shockwaves on and off the stone. An investigation was also conducted into the optimal position for "difficult" patients, *i.e.* the obese, patients with renal scarring, those who had undergone renal surgery and those with stones at less accessible intrarenal sites. The effect on stone clearance of treatment with the patient in the lateral position was assessed. Finally, a study was made of the effect on stone disintegration and clearance of such independent factors as obesity, the side and intrarenal site of the calculus, the clarity of the original ultrasound image, shockwave frequency and power and the choice of lithotriptor operator.

Patients and Methods

Between June 1987 and May 1989, 2688 lithotripsy treatments were performed on 872 patients (513 male and 359 female). Their mean age was 47.6 years (range 3–88). The stone sites and sizes are shown in Tables 1 and 2.

In all, 236 patients (27%) were considered moderately or severely obese. The 1031 renal calculi treated were located in 931 renal units, of which 256 (27%) were scarred and 407 (44%) had undergone either open or percutaneous surgery. Ureteric calculi for the purposes of this study were treated as "renal", since push/ESWL is our standard practice.

All treatments were performed by 1 of 9 urologists with no previous experience in ultrasonography. Each performed at least 100 treatments. The lithotriptor operator recorded data relating to the patient, the stone, imaging and treatment positions, the quality of the ultrasound image factors, shockwave power and frequency, discomfort experienced by the patient, altered sound pitch on focusing shockwaves on and off the stone, and alterations in ultrasound image following treatment. These data were recorded for each treatment on multiple choice record sheets and stored in a computer database.

Percentage stone disintegration was assessed by a plain X-ray taken immediately following treat-

Table 1 Stone Sites

Site	*No*	*(%)*
Renal pelvis	194	(16.7)
Renal calix	789	(68.1)
Staghorn	48	(4.1)
Ureter	128	(11 1)
Total	1159	

Table 2 Stone Sizes

Size (mm)	*No.*	*(%)*
<10	757	(65.3)
10–20	314	(27.1)
21–40	68	(5.9)
>40	20	(1.7)
Total	1159	

ment and percentage stone clearance by a film at least 2 weeks later. A single assessor (E.A.K) examined all X-rays. The significance of each factor in relation to the results of treatment was assessed using a comprehensive microcomputer-based statistics package. The P values are from a χ^2 test with various degrees of freedom. The data were further analysed using log linear modelling techniques.

Results

The mean time taken for stone imaging and positioning gradually lessened (from 11.2 min for the initial 3 months to 7.5 min for the final 3 months). Percentage stone disintegration, clearance and stone-free rates (no visible stone material on conventional radiography) are shown in Table 3. There was no significant difference in the percentage stone disintegration or clearance obtained by the various operators at the 5% level.

Fifty-nine percent of all patients were successfully imaged and treated in the supine position but in the remaining 41% this was not possible and improved stone imaging was achieved with the patient in a lateral position; 56% of obese patients and 55% of those with stones in the renal pelvis were more satisfactorily imaged in a lateral position. The supine position was satisfactory for 69% of right upper caliceal stones and 68% of stones in the lower calices (Table 4). There was no significant overall difference in the percentage of individual stones disintegrated or cleared following treatment in the supine or lateral position, but significant differences were found in subgroups of stones. The percentage disintegration of the largest renal pelvic stones and the percentage clearance of the smallest caliceal stones were significantly greater when the patient was treated supine (Tables 5 and 6).

A reduction in shockwave power was required in 16.2% and frequency in 7.3% of treatments to achieve satisfactory tolerance of the procedure by the patient.

Significant factors associated with improved stone disintegration and clearance were pain during repositioning of the shockwave generator, attenuation and widening of the acoustic focus and widening of the acoustic shadow as assessed by the operator on completion of an individual treatment. Renal scarring and a history of previous renal surgery were associated with improved stone disintegration but not clearance. Changes in the reflected sound were not associated with changes in disintegration or clearance, nor were other factors such as the side or intrarenal site of stone, obesity, the quality of the original ultrasound image factors and shockwave frequency or power.

Discussion

Chaussy *et al.* (1984) were the first to report on the clinical use of ESWL; they considered using ultrasound imaging but found it unsatisfactory and opted instead for biplanar fluoroscopy. However, in addition to the undesirable exposure of patients and staff to radiation, fluoroscopy severely limited the use of ESWL in biliary lithotripsy. The advent of improved ultrasonics and lithotriptor design enabled real-time ultrasound imaging to be successfully used in biliary and urinary lithotripsy (Marberger *et al.*, 1988; Vallancien *et al.*, 1988; Ferrucci, 1989; Kiely *et al.*, 1989). As a result, urologists wishing to use these lithotriptors need to become adept at renal ultrasonography and, in particular, be able to detect the subtle ultrasound image changes produced during extracorporeal lithotripsy. This report confirms their ability to do so.

Table 3 Stone-free Rates and Mean Percentage Disintegration and Clearance of Renal Calculi

Site	*Size (mm)*	*No*	*% Stone-free*	*Mean % disintegration*	*Mean % clearance*
Renal pelvis	<20	112	71	81	76
	21–40	82	22	51	43
Staghorn	20–40	21	32	44	39
	>40	27	17	36	30
Upper calix	<20	174	62	75	71
	21–40	15	0	49	44
Middle clix	<20	205	79	80	79
	21–40	15	0	49	42
Lower calix	<20	358	72	84	73
	21–40	23	25	57	47

Table 4 Percentage of Treatments in Supine and Lateral Positions

All patients		*Supine (%)* *(59%)*	*Lateral (%)* *(41%)*
Upper caliceal stones:	Left	59	41
	Right	69	31
Lower caliceal stones		68	32
Renal pelvic stone		45	55
Obese patients		44	56

Table 5 Significance of Differences in Percentage Stone Disintegration following Treatment in Supine and Lateral Positions

Site	*Size (mm)*		
	<10	*11–20*	*>20*
Renal pelvis	N.S.	N.S.	$P<0.05$*
Calix	N.S.	N.S.	N.S.
Ureter	N.S.	N.S.	–
Staghorn	–	–	N.S.

N.S. Not significant

* Where disintegration is supine position was greater

Table 6 Significance of Differences in Percentage Stone Clearance following Treatment in Supine and Lateral Positions

Site	*Size (mm)*		
	<10	*11–20*	*>20*
Renal pelvis	N.S.	N.S.	N.S.
Calix	$P<0.05$*	N.S.	N.S.
Ureter	N.S.	N.S.	–
Staghorn	–	–	N.S.

* Where clearance in the supine position was greater.

The gradual reduction in the time taken for stone imaging and positioning from 11.2 to 7.5 min over a 2-year period underlines this point. During this period, several new personnel began using the EDAP LT.01 without affecting this trend. In addition, the absence of significant differences between percentage rates of stone disintegration and clearance for the various operators implies a consistent level of competence.

Certain patients and some stones at certain sites present a greater challenge than others. Upper caliceal stones (particularly on the left side) may be masked by ribs. Other problems have been obese patients, renal scarring, previous renal surgery and certain renal pelvic stones. The excellent manoeuvrability of the processing head of the EDAP LT.01 allows orientation in every direction and helps to overcome these problems. During the initial 18 months a 5 MHz ultrasound transducer was used. This was replaced by a 3.5 MHz transducer which produces clearer images of deeper structures and is an advantage in more obese subjects.

Imaging of the obese patient or the patient with a renal pelvic stone may often be facilitated by using a lateral position. This probably results from the reduction in tissue interposed between stone and transducer. In the case of the pelvic calculus, lateral imaging also allows a "window" through the kidney and "lifts" the stone anterior to the transverse processes and psoas muscle to facilitate visualisation. A disadvantage of the lateral position is that the body weight is taken almost totally by the hip and shoulder, with the "gap" in the lithotriptor table making this position more difficult to maintain over a prolonged period. Slight movements by the patient during treatment may allow the stone to escape from the focus and explain both the reduced percentage clearance of small caliceal stones and disintegration of large pelvic stones.

Following ESWL, the 3 features of the ultrasonic stone image (attenuation and widening of focus and widening of acoustic shadow) were graded under 4 headings ranging from "no change" to "excellent". The operator's assessment of these factors was found to reflect stone disintegration and subsequent clearance. This supports the view that the operator's judgement is a reliable guide to when an individual stone is disintegrated and can therefore dictate the end-point of a lithotripsy session. It does not mean, however, that conventional X-ray evaluation can be abandoned for subsequent follow-up. "Stone-free" on conventional X-ray must remain the comparative gold-standard of successful ESWL. In addition, while silent or symptomatic migration of stone fragments or "Steinstrasse" to the ureter may be inferred by detecting hydronephrosis on ultrasonography, the plain abdominal X-ray is mandatory in clinical assessment.

As further evidence of correct stone imaging and positioning, the pain produced by readjustment of the processing head was also significantly associated with the degree of stone disintegration and clearance. This probably resulted from the tiny focus of the piezoelectric lithotriptor causing little discomfort when centred on the energy-absorbing stone but resulting in pain when surrounding tissues were struck.

The alteration in the reflected sound produced during minor adjustment of the processing head was unhelpful in predicting the success of the treatment. We have recorded and digitally analysed these signals and found clear discrimination between shockwaves striking either the calculus or the surroundings in both *in vivo* and *in vitro* studies (Ryan *et al.*, 1989). Although the human ear is not sensitive enough to distinguish such alterations, sophisticated recording devices are able to do so and this facility may be incorporated as an extra imaging and "stone-tracking" aid in future lithotripsy design.

Renal scarring and previous renal surgery were associated with a significantly greater percentage of stone disintegration but not clearance. This may be due either to interference with the passage of stone debris by alteration of the renal architecture or to rapid stone reformation in pathological kidneys.

Other factors not associated with altered stone disintegration or clearance were intrarenal site, obesity and the frequency or power of shockwave.

Unlike other authors (Drach *et al.*, 1986; Vallancien *et al.*, 1988), we found no reduction in the clearance of stones from the lower calcies. This may be because our patients are advised to drink large quantities of fluids and to practise a form of postural drainage for at least 24 h following treatment.

The pressure at the shockwave focus depends on the tissue interposed between the shockwave generator and the focus (Gunasekeram *et al.*, 1989). Although a reduction in stone disintegration might be expected in the obese patient, this stone disintegration did not occur. In addition, reductions in shockwave frequency or power, required because of the patient's discomfort, did not influence stone disintegration. Such reductions rarely fell below 65% of maximum power. Previous recordings of the pressures generated at the focus of the EDAP LT.01 showed that the increase in pressure as the power of the shockwaves rises almost ceases at approximately 65% of maximum power (unpublished data). It therefore appears that even at reduced power and in obese subjects, shockwave pressure remains above the threshold required for the disintegration of calculi.

The literature abounds with the latest results of ESWL from various centres using differing lithotriptors. We have investigated the subjective impressions formed since we began using the EDAP LT.01 as to how particular patients and stones are best managed. Some of these impressions were false, but others have been confirmed, including our ability to estimate by ultrasound when stone disintegration occurred and the superiority of lateral imaging for obese patients and renal pelvic stones. This study has also confirmed that the urologist can quickly become adept at ultrasonography and he should not hesitate to widen its application to everyday practice.

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The Authors

E A. Kiely, MCh, FRCSI, Senior Urological Registrar, Meath Hospital

D. Madigan, BA, PhD, Honorary Research Fellow, Irish Stone Foundation.

P. C Ryan, FRCSI, formerly Senior Urological Registrar, Meath Hospital. Now Senior Urological Registrar, Mater Hospital Dublin.

M R Butler, BSc, FRCSI, FRCS, Consultant Urologist, Meath Hospital.

Requests for reprints to: M R. Butler, Department of Urology, Meath Hospital, Heytesbury Street, Dublin 8, Ireland

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Morphostructural Patterns in Staghorn Renal Calculi seen under the Scanning Electron Microscope

A. NAVARRO, A. CAMPOS, P. V. CRESPO, A. ZULUAGA, T. RODRÍGUEZ and J. AGUILAR

Urology Service, University Hospital of Granada; Departments of Cell Biology and Pedology, University of Granada, Granada, Spain

Summary—A total of 43 surgically removed staghorn urinary calculi were examined under a scanning electron microscope; the findings, together with microanalytical data, were used to determine morphostructural patterns corresponding to different mineral compositions. The stones were classified into 3 groups: phosphatic, urate and cystine.

Scanning electron microscopy (SEM) is one of the many analytical procedures currently used in the study of urinary lithiasis. Among the pioneers in this technique, Boyce (1972) and Alonso and Somacarrera (1972) described some of the main ultrastructural features of urinary calculi. Since then, our knowledge has increased as more experience was gained with SEM analysis (Dodlsch and Koestel, 1975; Kim, 1982; Cifuentes, 1984).

Staghorn urinary calculi, because of their shape and effect on renal function (alone and in association with urinary tract infection), represent one of the most troublesome types of lithiasis encountered in clinical practice. Recent advances in lithotripsy, both extracorporeal and via endoscopy, have made these techniques the therapy of choice. Detailed information on the composition and structure (*i.e.* hardness, consistency, friability, etc) of these stones would aid in selecting the most effective therapeutic approach. In this study, various crystalline structural types were correlated with the chemical composition of staghorn calculi, making it easier to predict the consistency of the stone and thus select the treatment most likely to succeed in fragmenting and removing it.

Material and Methods

We examined 43 staghorn renal calculi removed during surgery in the Urology Service of the University of Granada Hospital. All stones were sectioned through peripheral, intermediate and central zones to obtain slices not exceeding 5 mm in diameter, which were then covered in gold (Polaron E-5000 sputter coater) and observed in a Philips 505 scanning electron microscope equipped with an EDAX (X-ray dispersive energy analysis) system for morphological studies. Microanalysis was performed on carbon coated specimens (Panessa, 1974). The microanalyses were performed on averages from 2 measurements expressed as counts/50 s, taken in the peripheral, intermediate and central zones (Tables 1 and 2). For semiquantitative analyses, all data were transferred upon measurement to a computer and corrected using the ZAF component (Z = atomic number of the element being analysed, A = absorption, F = secondary fluorescence) of the EDAX system. This establishes the percentage content of the elements under study (Boekestein *et al.*, 1983).

Briefly, the microanalytical technique involves bombarding the sample with a fine beam of electrons to generate X-rays at the points of impact. These X-ray patterns are characteristic for each element and produce a variable spectrum of intensities proportional to the dispersive energy. Different elements in the material can thus be identified on the basis of the resulting spectra. Different radiation intensities give rise to electric impulses whose amplitude is proportional to their energy. These impulses are then amplified and transmitted to a multichannel analyser and digital

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Table 1 Microanalytical Data from Staghorn Cystine Urinary Calculi with a Calcium-based Outer Layer

Element	*First measurement CPS**	*Second measurement CPS*	$\bar{X}$ *CPS*	*ZAF %†*
Peripheral zone				
Na	3.180	1.400	2.29	1.08
S	591.542	521.169	556.35	95.25
Ca	17.919	—	—	—
Intermediate zone				
Na	1.140	1.800	1.62	0.85
S	530.979	492.688	511.833	99.15
Central zone				
S	504.518	495.041	499.766	100.00

*CPS = counts per second, the unit used to quantify the X-ray dispersive energy of each element in the sample when struck by an electron beam.

†ZAF = semiquantitative analysis program used to calculate the percentage content of each element in the sample. Z = atomic number of the element in question. A = absorption. F = secondary fluorescence.

computer for identification and semiquantitative analysis.

Results and Discussion

Of the renal calculi studied, 30 were phosphatic, 6 were urate, 2 were cystine and 5 were of mixed composition. Scanning electron microscope observations and microanalytical data revealed further differences.

Phosphatic calculi

As previously noted by Kim (1982), phosphatic stones consisting of a single element were rarely encountered in SEM images. In any given stone there were usually several different phosphatic compounds, combined in some cases with ammonium acid urate crystals. The following components were identified.

Table 2 Mean counts per second and ZAF Corrected Values Obtained from Microanalysis of Cystine Urinary Calculi

Element	$\bar{X}$ *CPS*	*Total ZAF %*
Na	2.100	1.08
S	522.644	95.64
Ca	5.973	2.28

See footnotes to Table 1 for abbreviations.

Struvite crystals were seen in the shape of trapezoidal prisms similar to the "coffin lid"-shaped magnesium ammonium phosphate crystals found in urinary sediment.

Defective forms were found more often than perfect crystals, as noted in an earlier study (Dodlsch, 1975). Some slices showed cracks which under low magnification formed a reticular pattern recalling cerebral convolutions (Fig. 1).

In some specimens struvite had become trimagnesic orthophosphate (Fig. 2), a form characterised by laminar structures as described by Cifuentes (1984).

Hydroxyapatite normally appears as slender, radially arranged needles. However, in our staghorn calculi the characteristic pattern of crystals described by Pinto (1976) was not apparent. Instead of dense bundles of crystals stacked in thin, elongated hexagonal laminas, the hydroxyapatite was predominantly microgranular.

In accordance with Konjiki (1980) and Aguilar (1984), our findings suggest that the role of hydroxyapatite in calculi is to cement struvite crystals together. A similar effect has also been proposed for carbonate-apatite and ammonium acid urate in infectious calculi.

Under SEM, carbonate-apatite was composed of mushroom- or crescent-shaped spherulites of variable size, although most measured approximately 7μ in diameter. Glomerular aggregates of smaller spherules (Fig. 3) were also seen.

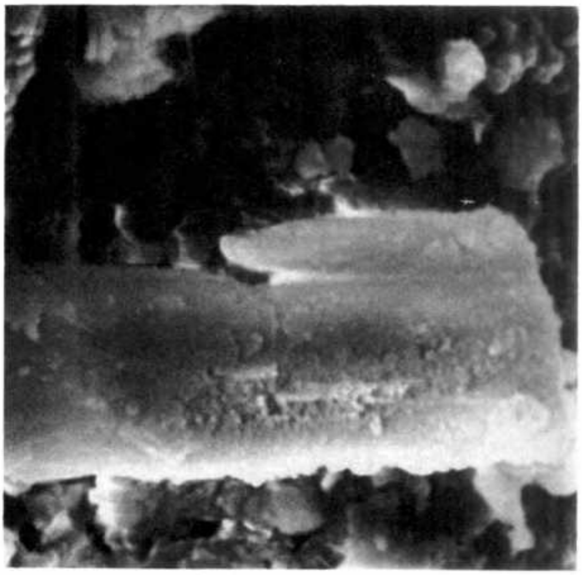

Fig. 1 Convoluted struvite from a staghorn urinary calculus. (×1250).

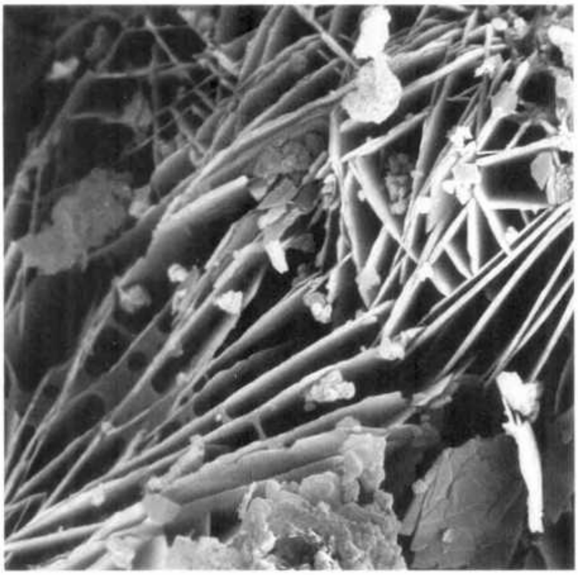

Fig. 2 Fine laminar structure in a trimagnesium orthophosphate calculus. (× 2600).

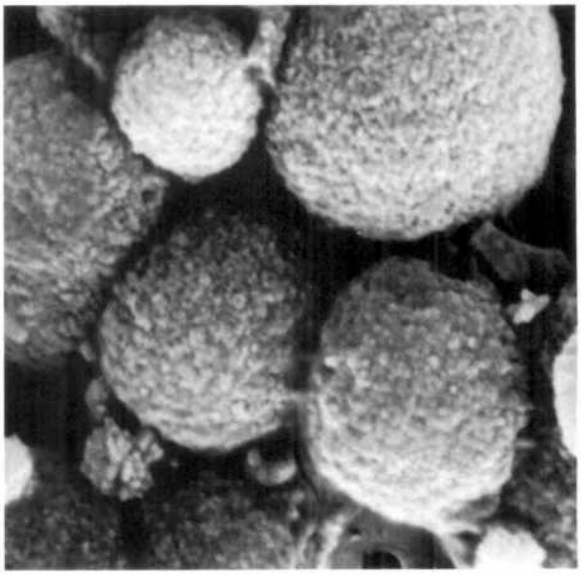

Fig. 3 Detail of spherular apatite formations. (× 6500).

Brushite appeared as pseudocolumnar or radially arranged crystals whose splintered, pitted surface presumably contained an organic matrix (Fig. 4). Ambruster (1979) described brushite crystals similar in appearance and arrangement to those in our staghorn calculi, but Cifuentes (1984), in addition to these forms, observed relatively large blocks of crystals which were absent in our material.

In phosphatic calculi, calcium phosphate was found in different regions, including the nucleus, pores, on the surface or disseminated throughout the stone. Like struvite, however, it was seen predominantly in the centre of the calculus. The high percentage of calcium phosphate located mainly in the central nucleus, as determined by EDAX analyses, suggests that a phosphocalcic nucleus acted as the centre of crystallisation for the formation of the calculi.

Urate calculi

Under SEM, anhydrous uric acid showed a variety of crystallisation patterns, although the most common form consisted of randomly scattered prisms that varied in size. Some slices showed a disorganised mode of association, while others exhibited lanceolate crystals whose apex was in some cases truncated. These shapes were seen in laminar, branched growths (Figs 5 and 6) in which the lanceolate structures appeared to form buds of uric acid arranged in a spiral fashion along the "branches".

Uric acid crystals varied markedly in size from one layer to another, larger crystals often alternating with smaller ones.

Ammonium acid urate presented radial patterns under SEM. The needle-shaped or fibrillar crystals formed easily distinguishable bundles radiating from a central point (Fig. 7). Microanalysis failed to detect any unusual elements. Ammonium acid

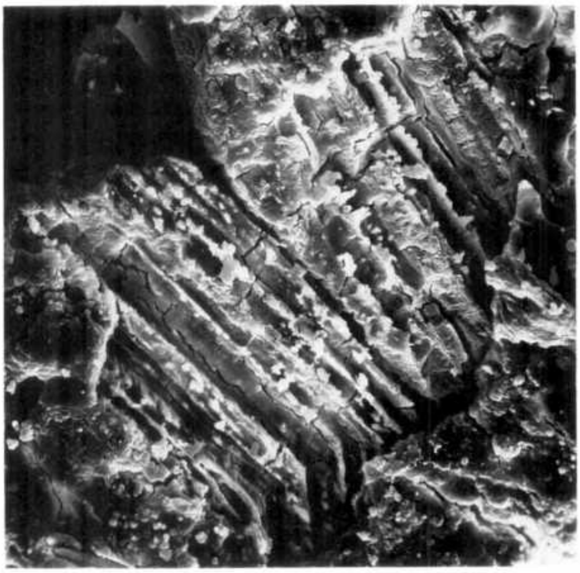

Fig. 4 Columnar bundles of brushite from a staghorn calculus. (× 480).

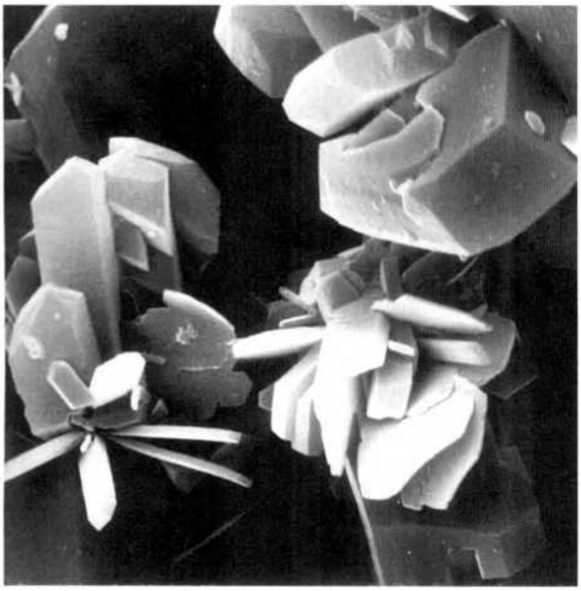

Fig. 5 Radial uric acid formations from a urate staghorn calculus. (× 3750).

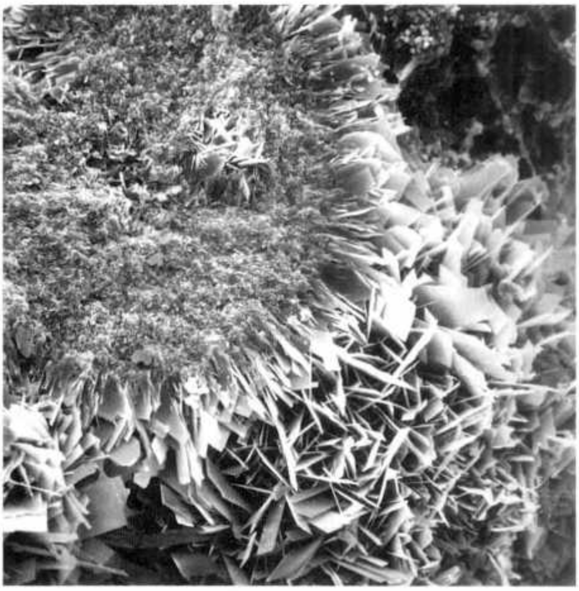

Fig. 7 "Pincushion" formation of ammonium acid urate from a staghorn calculus. (× 500).

urate was not the sole component of this type of calculi, but rather a minor component.

Monosodium urate was found radiating from a central hub. Kim (1982) also described this compound as arranged in step-like or scale-like overlapping laminas.

Cystine calculi

Under SEM, cystine calculi were composed of small, tightly packed prisms which showed a tendency to form structures of a higher order (Fig. 8). The characteristically perfect hexagons seen in urinary sediment under light microscopy were not

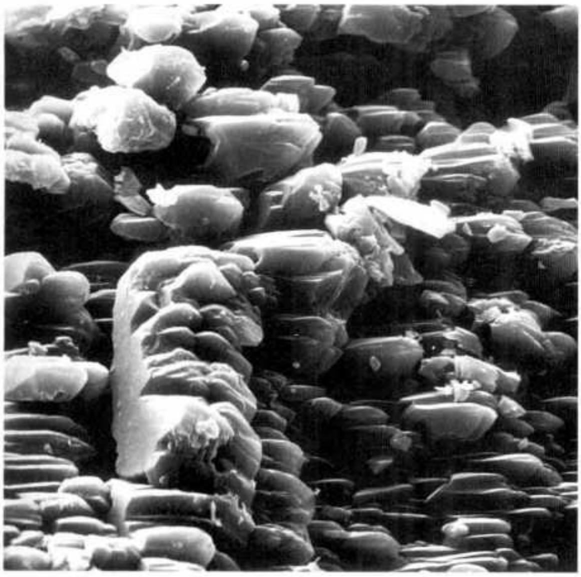

Fig. 6 Uric acid in palisade formations, from the same uric acid stone as in Fig. 5. (× 1490).

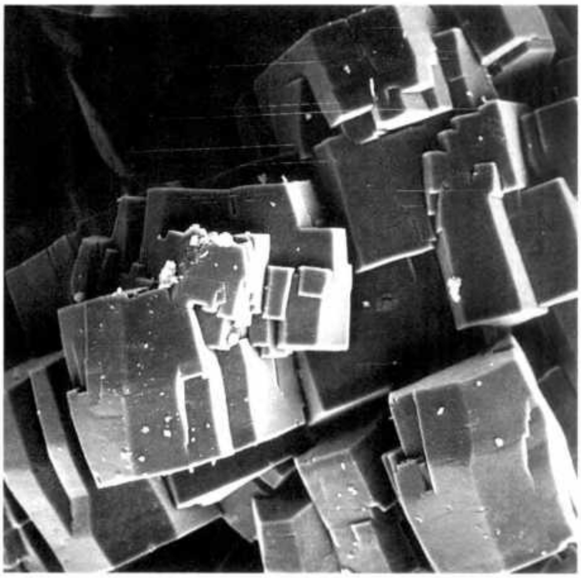

Fig. 8 Prismatic formations in a cystine stone. (× 200).

Table 3 Morphostructural Patterns in Staghorn Renal Calculi seen under Scanning Electron Microscope

Composition	*Morphology*
Struvite	Trapezoidal, convoluted
Apatite	Spherular
Brushite	Fan-shaped columnar prisms
Trimagnesic orthophosphate	Thin laminas
Ammonium urate	"Pincushion" formations
Uric acid	Palisade, prismatic and floral formations
Sodium nitrate	Radial
Cystine	Aggregates of hexagonal prisms

apparent in our material owing to crystalline aggregation. According to Cifuentes (1984), complete development of hexagonal crystalline prisms is not always possible in this type of calculus because of space limitations which occur when the growing crystals interfere with each other's expansion.

Of the 5 calculi of mixed composition, 4 contained uric acid together with different compounds: carbonate-apatite + struvite + ammonium acid urate + weddelite; whewellite; whewellite + weddelite; ammonium acid urate + sodium urate + weddelite (1 of each); the remaining calculus consisted of struvite + ammonium acid urate + sodium urate.

Scanning electron microscope observations of staghorn renal calculi showed 11 morphostructural patterns (Table 3). Further characterisation of these topographical types by microanalysis allowed us to determine basic mineralisation indices.

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The Authors

A. Navarro, MD, PhD, Specialist in Urology.
A. Campos, MD, PhD, Chairman, Department of Cell Biology.
P. V. Crespo, MD, PhD, Professor, Department of Cell Biology.
A. Zuluaga, MD, PhD, Surgeon and Director, Urology Service.
T. Rodríguez, PhD, Professor, Department of Pedology.
J. Aguilar, PhD, Chairman, Department of Pedology.

Requests for reprints to: A. Navarro Sánchez-Ortíz, c/ Martínez Campos 2, 6 izda, E-18005 Granada, Spain.

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^{99m}Tc DTPA Diuretic Renography in the Evaluation of Surgery in Chronic Schistosomal and Non-schistosomal Obstructive Uropathy

R. H. BAHAR, M. SABHA, K. KOURIS, K. E. BRITTON, Y. M. ALI, M. AWDEH, H. M. ABDEL-DAYEM and T. NILSSON

Departments of Nuclear Medicine and Surgery, Faculty of Medicine, University of Kuwait and Ministry of Public Health, Kuwait; Department of Nuclear Medicine, St Bartholomew's Hospital, London

Summary—The selection of patients with chronic obstructive uropathy for surgery is difficult because of problems in identifying true obstruction in a grossly dilated urinary tract. This is especially so in schistosomal (bilharzial) obstructive uropathy.

A prospective study of 90 patients (68 with chronic schistosomal and 22 with non-bilharzial obstructive uropathy) was carried out. All patients underwent pre-operative and post-operative radionuclide ^{99m}Tc DTPA diuretic renography (RDR). The aims were to assess the value of RDR in the pre- and post-operative management of these patients and whether it could predict the outcome of surgery.

Distinctive renogram patterns were identified in patients who required surgical management. These were found useful in monitoring the results and in predicting the outcome of surgery.

The majority of patients in this study had chronic schistosomal obstructive uropathy. Urinary schistosomiasis (bilharziasis) is caused by *Schistosoma haematobium* and it affects approximately 200 million people throughout the world. The disease is endemic in many Middle Eastern and Central African countries such as Egypt, Iraq, Yemen and Zimbabwe (Warren, 1985). The incidence in Kuwait is quite high because of immigrant labour from affected areas (Forsyth and Hughes, 1973).

Urinary schistosomiasis produces various abnormalities in the urinary tract. The most frequent lesion is bilateral pelvicaliceal and ureteric dilatation (Umerah, 1977, 1981; Hussain *et al.*, 1980; Young *et al.*, 1984). The dilated ureter may become obstructed at the lower end by a stricture, a stone or bilharzial papilloma (Kazim, 1987). The cause of gross dilatation in such a ureter, in the absence of an obstructive lesion, is thought to be due to disorganised ureteric peristalsis, itself the result of damage to the periureteric and perivesicular fibrous sheath caused by heavy infestation with ova (Umerah, 1977, 1981; Hussein *et al.*, 1980). These urinary systems should not be labelled as mechanically or functionally obstructed since there appears to be no increase in the resistance to flow which is required for the definition of obstruction (Britton *et al.*, 1987). They should be described as dilated non-obstructed urinary tracts.

In general, the selection of patients with dilated urinary tracts for surgery is a difficult task. This is especially true in schistosomal patients (Hussain *et al.*, 1980; Kazim, 1987).

The aims of this study were to compare pre-operative ^{99m}Tc DTPA RDR with the surgical findings and clinical follow-up of these patients in order to assess the value of RDR in their management and whether it can be used to predict the outcome of surgery.

Patients and Methods

Ninety patients (95 operations) were studied prospectively, 68 with schistosomal obstructive uro-

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pathy. These 68 patients came from endemic areas and had a history of chronic schistosomal uropathy with urinary symptoms suggestive of obstruction. All underwent intravenous urography (IVU), but only 21 results were available. Only 29 patients had urodynamic renal flow and pressure studies (the Whitaker test) (Whitaker, 1976a). All had RDR 1 to 3 weeks prior to the operation and 1 to 4 months post-operatively.

Technique of Radionuclide Diuretic Renography

The hydrated patient (150–200 ml) was seated with his back resting on the face of a large field gamma camera (GE 500A) fitted with a low energy general purpose collimator and linked to a mini-computer (GE Star). A bolus injection of 4–10 mCi (148–370 MBq) ^{99m}Tc DTPA was given through an intravenous cannula and was flushed with normal saline. A 2-phase dynamic study was performed: (a) perfusion phase: 1 s/frame for 1 min; (b) renographic phase: 20 s/frame for 29 min; 40 mg frusemide were given intravenously at 16 to 18 min. Post-void static images were obtained at the end of the study.

Processing was carried out using a locally developed computer protocol which calculates various parameters, including GFR and time activity curves for the whole kidney, parenchyma and pelvis (Kouris *et al.*, unpublished material). Deconvolution analysis was used in a few patients and its results are under current evaluation.

Interpretation of the results

The observers first assessed the analogue sequential renal images and recorded data on the size and shape of the kidneys and retention of tracer in the pelvicaliceal systems and ureters; the effect of frusemide on urinary retention was also noted. The time activity curves (TACs) were studied and other parameters, such as individual kidney uptake, glomerular filtration rate and transit times, were recorded.

Analysis of Time Activity Curves

Bahar *et al.* (1988) identified the following abnormal functional TAC patterns seen during renography (Fig. 1):

F1 Slightly delayed excretion, good peak, good descent of the curve, no need for frusemide. This pattern represents mildly dilated pelvicaliceal systems.

F2 Delayed excretion, poor peak, good response to frusemide. This represents moderately dilated pelvicaliceal systems.

F3 Delayed excretion, no peak (rising curve), adequate response to frusemide. This represents grossly dilated non-obstructed pelvicaliceal systems.

F4 Delayed excretion, no peak (rising curve), poor or no response to frusemide. This represents an obstructed kidney.

F5 Slight uptake (more than background) followed by plateau curve and no response to frusemide. This represents severe nephropathy.

F6 No uptake, the curve is similar to background. This represents an atrophic (absent) kidney.

In the presence of an abnormality, the observer must identify which of the above patterns best fits each particular TAC. Some patients with patterns F3, F4 and F5 underwent surgery but no surgery was performed in patients with patterns F1, F2 or F6.

Post-operative improvement in RDR was recorded as follows:

(a) A change in the size of the kidney and extent of activity on the analogue renal images.

(b) A change from one pattern to another, *e.g.* from F4 to F3 as shown by a better formation of the peak or a better response to frusemide; the slopes of the uptake and excretion parts of the TAC are useful quantitative parameters.

(c) An increase in split renal function and/or GFR on the affected side.

(d) An improvement in transit time(s).

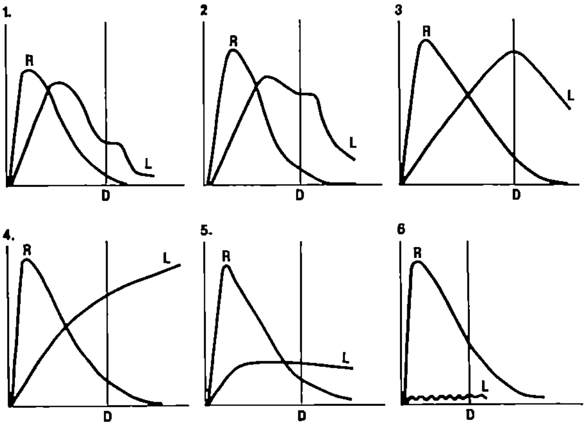

Fig. 1 Six functional patterns of radionuclide diuretic renography Vertical axis: activity Horizontal axis: time. R: right. L: left. D: time of injection of diuretic (frusemide).

Because there is no "gold standard", the results of RDR were correlated with clinical findings, IVU and the Whitaker test if available, surgical findings and 6 months' follow-up. Patients who showed improvement on RDR, IVU and clinical follow-up were considered to have benefited from the operation.

Results

The correlation of functional TAC patterns with findings at surgery is shown in Table 1; 95% of kidneys with pattern F4, 40% with F3 and 64% with F5 were found to be obstructed at surgery. The relation of these patterns to the outcome of surgery is shown in Table 2; 77% of patients with F4 (obstructed kidney), 40% of those with F3 (dilated non-obstructed) and 27% of those with F5 (severe nephropathy) showed an improvement regardless of the operation performed. Examples of such patients are shown in Figures 2 and 3. No patient with patterns F1 or F2 underwent surgery because they were considered to be non-obstructed. Similarly, no patient with F6 underwent surgery because the kidney was considered incapable of recovery. Reimplantation of the ureter to the bladder and ureterolithotomy gave a high rate of improvement (58 and 44% respectively). Balloon dilatation of the ureter gave an 83% improvement in a few selected patients. Because of the small number of patients involved, the results of the other operations were statistically less significant. However, percutaneous lithotomy and catheter dilation appeared promising (Table 2).

Table 1 Correlation of Functional TAC Patterns with Surgical Findings

TAC patterns	*Obstructed*	*Not obstructed*	*Total*
F3	11 (40%)	16	27
F4	51 (95%)	6	57
F5	7 (64%)	4	11
Total	69	26	95

Table 2 Relation between Radionuclide Diuretic Renography Functional TAC Patterns and Improvement following Surgery

Operation	*F3*	*F4*	*F5*	*Total*
Ureteric reimplantation	3/9*	19/27	1/4†	23/40
Lithotomy	5/10	8/10	1/2†	14/32
Balloon dilatation	2/4	8/8	0/0	10/12
Catheter dilatation	1/0	3/4	0/2	3/7
Pyeloplasty	0/2	1/2	0/0	1/4
Ileal conduit replacement	0/0	1/2	0/1	1/3
Nephrostomy	0/0	2/2	0/1	2/3
Percutaneous lithotomy	1/1	2/2	0/1	4/4
Total	11/27 (40%)	44/57 (77%)	3/11 (27%)	58/95 (61%)

*3 of 9 patients improved after surgery.
†Slight improvement

Interpretation of the time activity curves was the most efficient way to evaluate the surgical outcome in these patients. Twelve of the 58 patients who improved after surgery did not show any change in the size and shape of the pelvicaliceal systems on renography and yet there was a significant improvement in their TACs.

Split renal function did not change significantly in approximately half (56%) of the patients who showed a significant improvement in the TAC patterns (Table 3). Comparing RDR with IVU (only 21 were available), the IVU did not show any change in 8 patients in whom there was a definite change in the RDR TACs. The Whitaker test was available in only 29 patients. In 17 of them there was good agreement with the RDR findings but in the remainder there was disagreement between RDR and the Whitaker test. Ten patients had poor renal function (pattern F5) on RDR and the Whitaker test showed obstruction in 4 and no obstruction in 6. The 4 patients who were obstructed did not benefit from surgery. The other 2 patients had pattern F3 on RDR and the Whitaker test showed equivocal obstruction. Both failed to improve after surgery, which suggests that they were both unobstructed from the beginning.

Discussion

Identification of a significant obstruction in a patient with a grossly dilated ureter is a difficult problem. Schistosomal obstructive uropathy is a special case of grossly dilated ureter and pelvicaliceal system (Hussain *et al.*, 1980; Umerah, 1981;

Table 3 Correlation of Changes in Split Renal Function (% uptake) with Pre- and Post-operative TAC Patterns

Pre- and post-operative % uptake	*Correlation with TACs*	*No correlation with TACs*	*Total*
No change	20	36	56
Improved (increased)	14	8	22
Deteriorated (decreased)	8	9	17
Total	42/95 (44%)	53/95 (56%)	95

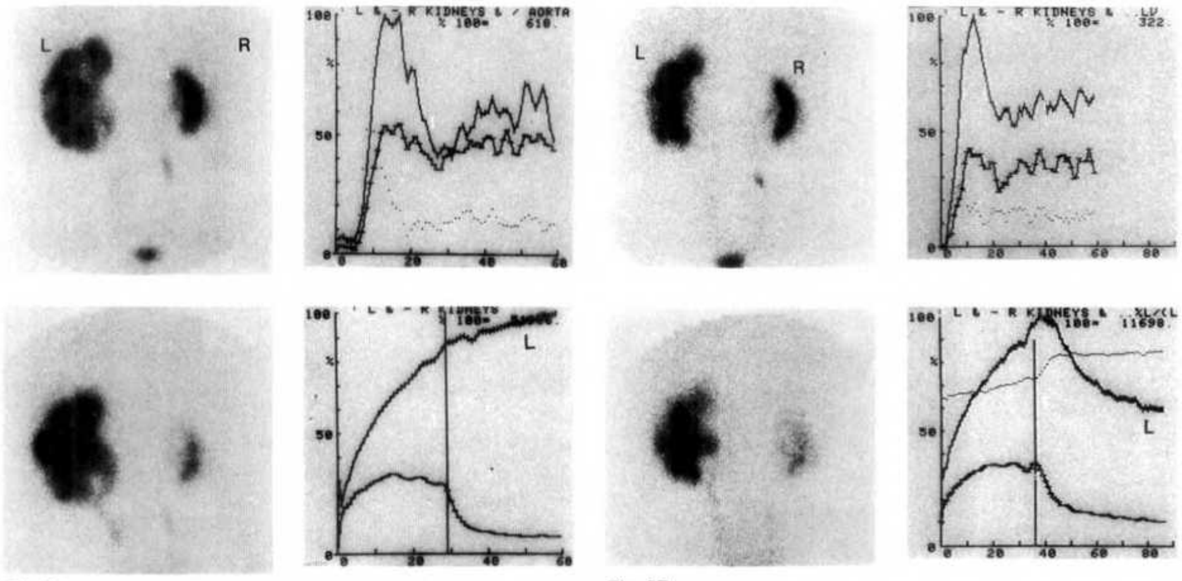

Fig. 2A

Fig. 2B

Fig. 2 Radionuclide ^{99m}Tc DTPA renography before and after surgery in patient with schistosomal obstructive uropathy. (A) Grossly enlarged and obstructed left kidney before surgery. (B) Marked improvement after surgery. Top left: image at 12 min. Bottom left: image 5 min after injection of frusemide. Top right: flow time activity curves over the first 60 s. Bottom right: kidneys' time activity curves. L: left. Vertical line: time of injection of Frusemide. (A) Left time activity curve is functional pattern F4. (B) Left time activity curve is functional pattern F3 showing correction of obstructive uropathy.

Young *et al.*, 1984) and in many cases the dilated ureter is not obstructed (Umerah, 1981; Young *et al.*, 1984). Lamki and Lamki (1981) and Bahar *et al.* (1988) have shown the usefulness of ^{99m}Tc DTPA renography in bilharzial patients.

In this study we have shown that RDR can be used to predict the outcome of surgery in these patients. The patterns reflect the various grades of resistance to the flow of urine as well as the transit time of the radiopharmaceutical and the volume of the dilated pelvicaliceal system (Zechmann, 1987). They also represent the responses of the kidney to various grades and periods of obstruction. Prolonged and severe ureteric obstruction is associated with pattern F5. F4 (corresponding to pattern II of O'Reilly *et al.* (1978)) was frequently associated with post-operative improvement because it represents true obstruction. This pattern was found to correlate well with true obstruction on urodynamic studies (Whitaker and Buxton Thomas, 1984) and with the operative findings (Table 1).

There are 2 reasons why only 77% of kidneys with pattern F4 improved after surgery. The first is related to difficulties at surgery. Many patients had undergone repeated reimplantation or catheter dilatation and some had double pathology, *e.g.* a stone plus a stricture. If the stone is removed the stricture remains. The second is related to the timing of post-operative RDR. A gradual improvement was noticed over 6 months, whereas many of these patients underwent RDR less than 5 weeks post-operatively.

Pattern F3 had a variable prognosis in some patients because it represents a grossly dilated system with insignificant or intermittent obstruction. In such cases an operation is advisable only for the relief of symptoms or removal of a stone. A urodynamic study is sometimes helpful and it can be either normal or abnormal (Whitaker and Buxton Thomas, 1984). This pattern corresponds to II/a of O'Reilly *et al.* (1978).

Pattern F5 is associated with a worse prognosis because it represents a severely damaged kidney which is unlikely to recover even if the obstructive lesion is removed.

Pattern F6 (atrophic kidney) implies no recovery after surgery and nephrectomy is usually recommended.

Because RDR provides physiological information on renal function it has been used to evaluate the outcome of surgery (Kalikaet *et al.*, 1981). However, Whitaker and Buxton-Thomas (1984)

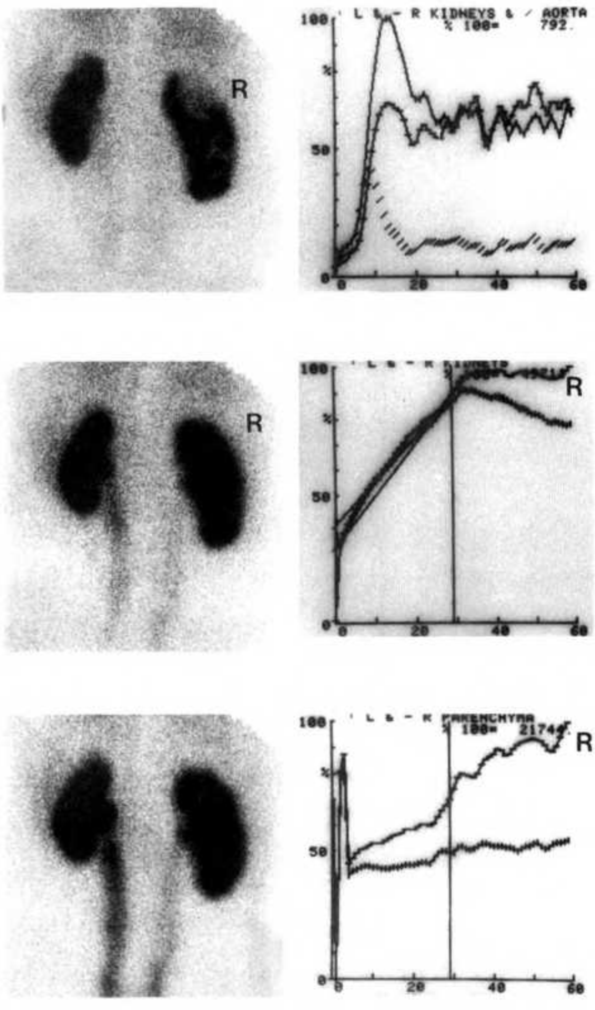

Fig. 3A

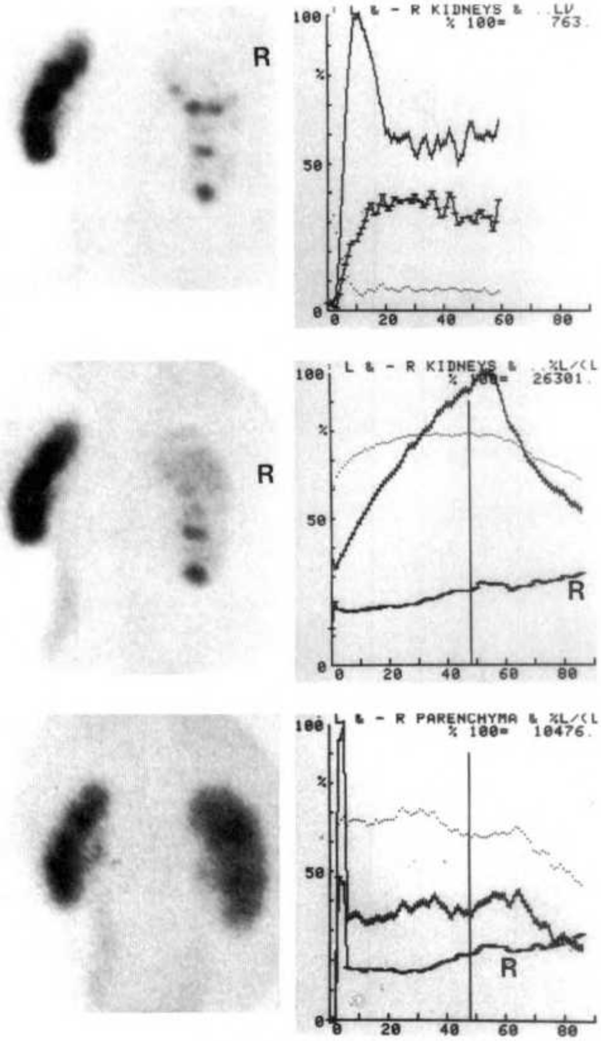

Fig. 3B

Fig. 3 Radionuclide diuretic ^{99m}Tc DTPA renography before and after surgery in a patient with schistosomal obstructive uropathy (A) pre-operatively, (B) post-operatively. Both kidneys showed functional pattern F3 before operation. The left kidney had balloon dilatation of the ureter and showed improvement in function after surgery. The right had no operation and showed deterioration in function. The time activity curve changed from F3 to F5.

Right row shows time activity curves of (lower) flow part (upper) and renographic part of RDR study. Left row shows the renal images: upper, 9 min after injection of ^{99m}Tc DTPA; middle, 5 min after diuretic injection; lower, after micturition.

found that 39% of patients had false negative and false positive results. Britton *et al.* (1987) attributed this to the following pitfalls of RDR:

(a) In the presence of poor renal function, frusemide has little or no effect on the damaged nephrons and therefore a non-obstructed dilated urinary tract may be reported as obstructed (*i.e.* false positive).

(b) In the presence of good renal function, a large diuretic response to frusemide may overcome the slight resistance imposed by a truly obstructive lesion and therefore an obstructed kidney may be reported as non-obstructed (*i.e.* false negative).

In such cases the parenchymal transit time index (PTTI) was found more useful in identifying obstruction and Britton *et al.* (1987) suggested that both RDR and PTTI should be used. We are currently evaluating this in bilharzial patients. The urodynamic pressure and flow study (Whitaker, 1976a,b), on the other hand, has many problems in these patients with dilated urinary systems (Pawer and Abdel-Dayem, 1986). These may be due to technical or physiological reasons.

The technical problems of the Whitaker test are that it is invasive, requires sedation and fluoroscopic or ultrasonic guidance in puncturing the pelvicaliceal system, and it is time-consuming in bilharzial patients. It is operator-dependent and extravasation of the infused fluid around the catheter may invalidate the study (Holden *et al.*, 1984). The recorded values of intrapelvic pressure in patients with grossly dilated pelvicaliceal systems and ureters may be due to pressure exerted by the surrounding organs or the muscular abdominal wall. Additional problems are created by dynamic pressure changes due to movement or repiration (Holden *et al.*, 1984).

The physiological problems of the Whitaker test are: the importance of measuring absolute resting pressure and relative intrapelvic pressure after infusion is still debatable (Mayo, 1983). The changes in relative intrapelvic pressure due to infusion of fluid may not be as relevant as the absolute resting pressure because the latter reflects the usual physiological situation (Holden *et al.*, 1984).

The resting pressure is dependent on nephron function and in a chronically dilated urinary tract it is usually almost normal because of physiological accommodation to the chronic effects of pressure (Biancani *et al.*, 1976). On the other hand, changes in intrapelvic pressure after infusion in a dilated and spacious system, as in bilharzial patients, may not be significant because such a system may accommodate the high infusion rate without significant change in the pressure despite the presence of significant obstruction. Furthermore, the operator does not know the required rate of infusion in such cases and the pressure changes thereafter reflect infusion rate and not the true situation. Thus the normal ranges for pressure and flow measurements for non-dilated systems may not apply to systems that are extremely dilated (Whitaker and Buxton Thomas, 1984). The Whitaker test does not provide information on renal function and is therefore unable to predict the outcome of surgery before such intervention in patients with significant nephron damage. Whitaker and Buxton Thomas (1984) considered this an advantage over RDR because it can identify obstruction in those patients with severe renal damage. However, in practice we have shown that there is no benefit from making this measurement in patients who would be unable to benefit from surgery.

In this study the time activity curves proved most useful in evaluating surgical outcome. Visual interpretation of the sequential renal images alone is unreliable. Split renal function and individual kidney GFR failed to show an improvement in many patients who showed clinical improvement, but the follow-up period may have been too short. These 2 parameters are calculated from the renogram time activity curve in the first 3 min and therefore do not reflect changes in the later phases which depend on the patency of outflow tracts and their volume, the trasit time activity in the parenchyma and pelvis as well as the uptake of the radionuclide.

^{99m}Tc DTPA radionuclide diuretic renography is a physiological test which provides information on the function of the kidneys and their response to outflow disorders; it also supplies morphological information on the kidneys and the urinary tracts. It is easier to perform than the Whitaker test and more accurate than intravenous urography. The 6 functional time activity curve patterns were useful in predicting the outcome of surgery and in the pre- and post-operative assessment of these patients.

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The Authors

R. H. Bahar, MB, ChB, MSc, Senior Registrar, Department of Nuclear Medicine, Mubarak Al-Kabeer Hospital, Kuwait.

M Sabha, FRCS, Consultant Surgeon, Department of Urology, Mubarak Al-Kabeer Hospital

K. Kouris, PhD, Senior Physicist, Department of Nuclear Medicine, Faculty of Medicine, Kuwait

K E. Britton, MD, MSc, FRCP, Physician in Charge, Department of Nuclear Medicine, St Bartholomew's Hospital, London

Y M. Ali, MB, ChB, MSc, Senior Registrar, Department of Surgery (Urology), Mubarak Al-Kabeer Hospital.

M Awdeh, BSc, Technician, Department of Nuclear Medicine, Faculty of Medicine

H M Abdel-Dayem, MD, Professor and Chairman, Department of Nuclear Medicine, Faculty of Medicine.

T Nilsson, PhD, Professor of Urology, Department of Surgery, Faculty of Medicine.

Requests for reprints to H. M Abdel-Dayem, Department of Nuclear Medicine, Faculty of Medicine, University of Kuwait, P. O Box 24923, Safat 13110, Kuwait

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Ultrasonography versus Intravenous Urography in the Evaluation of Patients with Microscopic Haematuria

A. ASLAKSEN, G. GADEHOLT and J. H. GOTHLIN

Department of Diagnostic Radiology, University of Bergen, Haukeland Hospital, Bergen, Norway

Summary—Urography and transabdominal ultrasonography of the urinary tract were compared in 193 patients with microhaematuria. Of 16 expansile lesions described at urography, 1 renal carcinoma was detected by both methods. Although the number of patients studied is too small for firm conclusions to be drawn, ultrasonography seems to offer advantages when compared with urography.

The evaluation of patients with microscopic haematuria has been a subject for debate over recent years. Such patients have usually been evaluated by means of intravenous urography (IVU) and cystoscopy in order to reveal occult disease. However, the value of IVU in the detection of tumours of the upper urinary tract has been questioned (Demos *et al.*, 1985; Glen *et al.*, 1989). Ultrasonography (US) has been reported to be sensitive in detecting hydronephrosis (Ellenbogen *et al.*, 1978), renal calculi (Juul *et al.*, 1987) and cysts (Weill *et al.*, 1987). The present investigation was performed to establish whether ultrasonography can replace IVU in the initial evaluation of patients who present with microscopic haematuria.

Patients and Methods

Over a 12-month period, 89 female and 104 male patients (aged 16–85 years, median 56) with microscopic haematuria, referred to the radiological department for IVU, were also examined by real time US of the upper and lower urinary tract. Patients with acute flank or abdominal pain lasting for less than 72 h were excluded. Five patients had an empty bladder at US and in 2 cases poor examination conditions did not permit reliable diagnosis of the left kidney.

IVU was performed with compression with an initial 24 × 30 cm zonogram over the kidney region, followed by a 35 × 43 cm film covering the kidneys and the bladder. Immediately after injection of contrast medium a 24 × 30 cm film was obtained over the kidneys. During compression a 24 × 30 cm film was obtained of the same region. Immediately after compression was released a 35 × 43 cm film was obtained (Göthlin *et al.*, 1986). Further radiograms were obtained in patients with impaired renal function due to obstruction. Metrizoate (Isopaque®, Nycomed, 440 mg iodine/ml) was used as the standard contrast medium in 177 patients. Iohexol (Omnipaque®, Nycomed, 300 mg iodine/ml) was used in 14 patients and ioxaglate (Hexabrix®, Guerbet, 320 mg iodine/ml) in 2 patients with additional risk factors, *e.g.* allergy or heart failure.

US was performed by 1 physician (A.A.) using a real-time scanner (General Electric RT 3000) with a 5 MHz sector phased array transducer (Weill *et al.*, 1987). The patients were examined in both the supine and the oblique position, preferably with a well distended urinary bladder. The examinations were recorded on videotape to enable review of the dynamic examination.

The urograms were handled as part of the normal routine in this department, *i.e.* they were interpreted by 1 consultant in the section of uroradiology. To mimic the clinical situation, the original reports were used for the comparison with US. Both the

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investigator performing US and the radiologist describing the IVU had access to the information given by the referring clinician. Each examination was performed without knowledge of the results of the other.

Hydronephrosis was defined by IVU as mild (subtle-to-obvious distension of the fornices or calices but the papillae still easily identifiable), moderate (calices ballooned outward and papillae barely visible) or severe (marked hydronephrosis with a sac-like collecting system) (Ellenbogen *et al.*, 1978). The various degrees of hydronephrosis at US were defined by measuring the maximum diameter of the calices: no hydronephrosis (0–5 mm), mild (6–10 mm), moderate (11–15 mm) or severe (> 16 mm) (Peake *et al.*, 1983). Calculi at US were defined as hyperechoic foci with a well defined acoustic shadow (Weill *et al.*, 1987). Suspected calculi at US with a diameter of 2 mm or less were not reported as positive findings. Duplication of the renal pelvis was suspected at US when there was a bridge of parenchyma with a renal cortex echo pattern splitting the pyelovascular central complex (Weill *et al.*, 1987).

Renal scarring was suspected at US and IVU when there was a focal thinning of the renal cortex. Major pyelonephritic changes at US were suspected when the kidneys were small with enhanced echogenicity and irregular surface.

The urological findings were divided into 3 categories according to Carson *et al.* (1980). Highly significant lesions were defined as those that constituted a threat to the patient's life or required a major surgical procedure. Moderately significant lesions were those that were slightly life-threatening and they were usually treated medically. Insignificant lesions were mainly incidental findings and did not influence the management of the patient.

When there were multiple pathological findings in a patient, *e.g.* a simple cyst and a renal calculus, only the conditon with the highest clinical significance was taken into account.

Minor contrast media reactions were defined as mild nausea, chills, cough, fever and urticaria. Severe reactions were defined as circulatory shock, pulmonary oedema, bronchospasm and laryngeal oedema requiring hospitalisation. Feelings of warmth alone were not defined as a contrast media reaction.

Results

The diagnoses of neoplasms in the upper and lower urinary tracts are summarised in Tables 1 and 2. One renal tumour in the upper pole of the left kidney was diagnosed by both methods in a 75-year-old man. The tumour measured 7 cm in diameter and the diagnosis was confirmed by CT and histology of the resected specimen. Of the other 15 expansile lesions described by IVU, 12 exhibited all of the ultrasonic criteria of a simple cyst and in 3 patients no pathology was revealed either by US or CT.

The results of detecting calculi by US and IVU are summarised in Table 3. In 5 patients 1 ureter and 4 renal calculi, with diameters ranging from 5 to 10 mm, were overlooked by US. In another 9 patients IVU gave more information. In 5 of these, US suggested unilateral while IVU showed bilateral calculi.

In 5 patients with ultrasonically detected calculi, the urograms were interpreted as negative. One stone was lodged in the ureterovesical junction and 4 in the renal parenchyma or the pelvicaliceal system. The number of calculi in each patient ranged from 1 to 5 and their diameters from 2 to

Table 1 Sixteen Upper Urinary Tract Tumours Suspected at IVU. Comparision with US Findings

	IVU positive	*IVU negative*
US positive	1	1†
US negative	15*	—

* 12 cysts detected by US and 3 normal kidneys detected by US and CT.

† Angiomyolipoma 1 cm in diameter

Table 2 Lower Urinary Tract Tumours Detected by IVU and US in 3 Patients. The Findings were Verified by Cystoscopy and Histology

	IVU positive	*IVU negative*
US positive	1	1
US negative	1*	—

* Examined with an empty bladder

Table 3 Renal and Ureteric Calculi Detected by IVU and US in 30 Patients

	IVU positive	*IVU negative*
US positive	20*	5
US negative	5	—

* Urography detected more calculi in 9 patients and ultrasonography in 1

9 mm. In 1 patient, IVU reported a minor dilatation of the distal ureter and US showed a calculus in the ureterovesical junction.

Hydronephrosis detected by US and IVU is presented in Table 4. There was good correlation between the 2 methods in assessing the degree of hydronephrosis. In a 37-year-old man, IVU suggested a unilateral mild hydronephrosis and hydroureter (possibly because of the diuretic effect of contrast medium) and US was reported as normal. Findings of moderate and little significance are shown in Table 5.

Twenty-one patients had minor contrast media reactions, all with metrizoate (92% of all patients received metrizoate). There were no severe reactions.

Discussion

The prevalence of asymptomatic microscopic haematuria is reported to be between 1 and 13% (Mohr *et al.*, 1986). The condition is frequently detected with urine test sticks at routine examinations. Various algorithms, including cystoscopy, IVU, US, CT and angiography, have been proposed for follow-up.

Table 4 Hydronephrosis Detected by IVU and US in 9 patients

	IVU positive	*IVU negative*
US positive	8	0
US negative	1*	—

* Mild hydronephrosis detected by urography.

Table 5 Moderately Significant and Insignificant Lesions Detected by US and IVU

	Ultrasonography	*Urography*
Moderate		
Pyelonephritic scars	4	2
Bladder diverticulum	1	0
Bladder trabeculation	3	1
Enhanced renal echogenicity	4	—
Horseshoe kidney	0	1
Insignificant		
Simple cyst as sole finding	12	—
Double renal pelvis or ureter	2*	3
Pyelitis cystica	—	2
Malrotated kidney	1	1

* One false positive.

In a population based study, Mohr *et al.* (1986), found an incidence of 0.4% of upper urinary neoplasms. It is not stated which methods were used but a combination of IVU, US and CT is most likely. The patients were referred with asymptomatic microscopic haematuria; other causes, such as coexistent infections and abdominal pain, were excluded. In the present study the only exclusion factor was haematuria associated with acute flank or abdominal pain lasting for less then 72 h. No attempt was made to exclude other coexistent risk factors. However, the prevalence of pathology described by IVU in the present study is in accordance with that reported by Mohr *et al.* (1986).

The reason for referring a patient with haematuria to an imaging department is to discover potentially severe, ultimately life-threatening disease (mainly urological neoplasia). IVU has been considered the corner-stone in the detection of upper urinary neoplasms. In retrospective studies, however, Demos *et al.* (1985) and Glen *et al.* (1989) reported that small renal neoplasms could be overlooked by IVU. In the present study only 2 such tumours were discovered. A 7-cm renal carcinoma was discovered by both methods and a 1-cm angiomyolipoma, not necessarily life-threatening, was discovered by US alone.

Expansile lesions in the upper urinary tract were reported by IVU in 16 patients, but only 1 was a renal cancer. In a further 12 patients, with simple benign cyst as the sole finding on US, IVU was reported to be normal. Routine use of IVU in the examination of patients with microscopic haematuria should not be considered as a screening procedure in an otherwise healthy population. A positive predictive value of 6% in detecting renal tumours is a low value and would not have been accepted in other screening procedures such as mammography.

It is reported that US is sensitive in detecting urinary bladder tumours >5 mm (Brun *et al.*, 1984). The present study, however, was not designed to compare transabdominal US with cystoscopy in detecting tumours of the urinary bladder. Three neoplasms of the urinary bladder were detected by US and all were confirmed as malignant. US and IVU agreed in only 1 instance. A 4-cm tumour was detected by US only in a female patient whose main complaint was urinary frequency and recurrent urinary tract infection. One tumour detected by IVU was overlooked by US because the patient was examined with an empty bladder. This shows clearly that all patients referred for US should be examined with a distended bladder.

The detection of calculi in patients with haematuria may be a minor problem compared with the detection of tumours, but it is important to find reasons for the condition. Both US and IVU failed in detecting all calculi. Of the 5 stones overlooked by IVU, 3 patients had intestinal contents overlying one kidney and obscuring calculi, 1 had roentgen-negative calculi and 1 had a non-obstructing calculus lodged in the distal part of the ureter with multiple phleboliths on the plain radiogram. The main problem in detecting calculi on US is to distinguish structures in the echo-rich renal pelvis. Stone size, amount of subcutaneous fat, depth of the kidneys and focus of the acoustic beam are all crucial factors in producing a reliable acoustic shadow.

Using a computer model, Corwin *et al.* (1988) calculated large economic savings when replacing IVU with US as the initial radiological evaluation of patients with microscopic haematuria. Geitung *et al.* (1988) calculated the costs of IVU and US in this department. The cost of US was $65, IVU with high osmolar contrast media was $120 and with low osmolar contrast media the cost was considerably higher. The expense incurred in finding 1 renal carcinoma with US was $12,490; IVU with high osmolar contrast media cost $23,565 and with high osmolar contrast media almost twice as much. Even if all patients with hydronephrosis and calculi detected by US were re-examined with IVU, there would be substantial savings with a minimal loss of information.

No severe contrast media reactions occurred in the study group; statistically this was expected. Different mortality rates related to IVU have been reported. Using high osmolar contrast media, Hartman *et al.* (1982) reported a rate of 1:75,000 in a Mayo clinic series. Newer, low osmolar contrast media are more comfortable (fewer sensations of warmth and flushes), but the evidence for a higher degree of safety is still equivocal. No side effects are either reported or anticipated with US.

Unfortunately, the number of patients in this study is too small for any statistically significant differences to be revealed between US and IVU in the detection of upper urinary neoplasms. To detect 20 neoplasms one would have to examine 4000 patients with microscopic haematuria and in this district it would take 20 years to reach that number of patients. The solution to this problem could be a multi-centre study including a large number of patients with microscopic haematuria. The results of the present study, however, indicate that US might replace IVU as the initial examination of patients with microscopic haematuria; this would lead to great economic savings and minimal loss of information.

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The Authors

A. Aslaksen, MD, Research Fellow, The Norwegian Cancer Society.

G. Gadeholt, MD.

J. H Göthlin, MD, PhD, Professor

Requests for reprints to · A Aslaksen, Department of Diagnostic Radiology, Haukeland University Hospital, N-5021 Bergen, Norway.

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Bacteriological State of the Urine in Symptom-free Adult Males

I. D. SUGARMAN, L. J. PEAD, S. R. PAYNE and R. M. MASKELL

Department of Urology and Public Health Laboratory, St Mary's Hospital, Portsmouth

Summary—Mid-stream urine specimens from 120 symptom-free males aged between 15 and 60 years were examined for cells and bacteria. Only 3 specimens showed pyuria, all of which yielded fastidious organisms. No specimen yielded a pure growth of an aerobe. Fastidious organisms in pure or mixed growth were isolated from 26% of the specimens, none in a count $> 10^8$/l and the majority in counts $< 10^7$/l. It was concluded that pure growths of aerobes in any count in patients with symptoms are indicative of infection. Fastidious organisms should be sought in the urine of patients with symptoms or pyuria before more intensive and expensive investigations are pursued.

With a few rare exceptions, urinary tract infection is caused by commensal organisms, in particular those of the bowel and distal urethral flora, and diagnosis is bedevilled by the need to discriminate between contamination and infection of urine specimens. Adult males of all ages suffer from symptoms suggesting that urinary infection is far more common than is generally believed (Clarke *et al.*, 1985). Infections of the urethra and of the structures in communication with it, the prostate and epididymis, are as important clinically as those of the bladder and upper urinary tract. Such infections are likely to differ from bladder infections in 2 important ways. Firstly, aerobic pathogens, such as the Gram-negative coliforms, may be isolated from mid-stream specimens in low counts because, although causing tissue infection below the bladder, they may not extend to the bladder and thus not encounter the conditions which favour bacterial multiplication. Secondly, infection of tissues below the bladder may be caused by various fastidious species such as *Gardnerella vaginalis*, corynebacteria, chlamydiae and ureaplasmas. These organisms may be present in the urethral flora of symptom-free sexually active men and it therefore becomes necessary to discriminate between infection and contamination of the urine specimen.

In order to provide a yardstick against which the cellular and bacterial content of mid-stream urine from adult males with urinary symptoms may be compared, a study of males who had never suffered from symptoms suggesting either urinary tract infection (UTI) or urethritis was undertaken. The role of chlamydiae and ureaplasmas has been extensively studied by others and was outside the scope of the present investigation. Diagnostic facilities for detection of these organisms are not widely available in service laboratories to which urine specimens from men with frequency or dysuria are usually sent.

Patients and Methods

A total of 120 male volunteers, between the ages of 15 and 60 years, were sought. All were spoken to personally by one of the authors (I.S.) and asked to read a questionnaire (Fig.) before being included in the study. The questionnaire was phrased in such a way that if the volunteer could not take part in the trial he was not required to explain why.

Volunteers were sought both within the hospital (doctors, male nurses, laboratory workers, theatre staff) and other working environments (including ambulancemen, engineers). Those who decided to participate were then asked to produce a mid-stream specimen of urine (MSU). A full explanation

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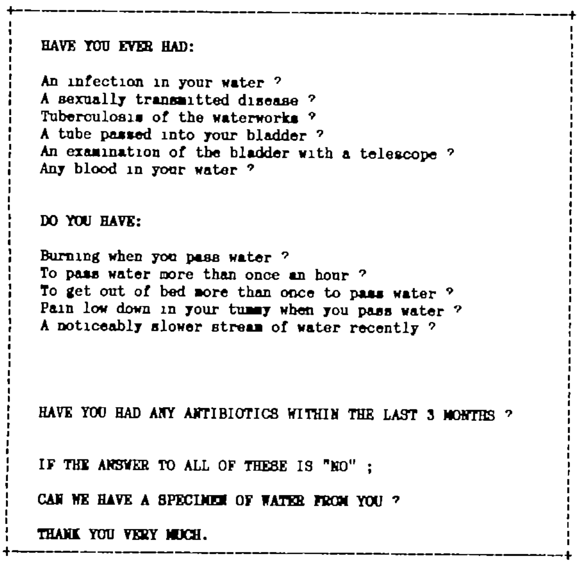

HAVE YOU EVER HAD:

An infection in your water ?
A sexually transmitted disease ?
Tuberculosis of the waterworks ?
A tube passed into your bladder ?
An examination of the bladder with a telescope ?
Any blood in your water ?

DO YOU HAVE:

Burning when you pass water ?
To pass water more than once an hour ?
To get out of bed more than once to pass water ?
Pain low down in your tummy when you pass water ?
A noticeably slower stream of water recently ?

HAVE YOU HAD ANY ANTIBIOTICS WITHIN THE LAST 3 MONTHS ?

IF THE ANSWER TO ALL OF THESE IS "NO" ;

CAN WE HAVE A SPECIMEN OF WATER FROM YOU ?

THANK YOU VERY MUCH.

Fig. Questionnaire used for selection of subjects

of this procedure was given; 71 specimens of urine were collected with no mention of withdrawing the foreskin, but from then onwards all volunteers were asked to withdraw the foreskin fully.

All specimens were taken to the laboratory for immediate microscopy and culture.

Uncentrifuged urine was examined using the inverted microscope technique (Maskell, 1982). Pyuria was defined as the presence of at least 10 WBC/μl. Specimens were inoculated using a 0.005 ml standard loop on to cysteine lactose electrolyte deficient (CLED) agar and chocolated blood agar (CBA) for incubation in 7% CO_2, and on to nalidixic blood agar (BANal) for anaerobic incubation. CLED and CBA plates were examined at 24, 48 and 72 h, anaerobic cultures at 48 and 72 h. Organisms were identified using standard procedures. All bacteria isolated were recorded. Recognised Gram-negative aerobic urinary pathogens were recorded as aerobes and identified. Organisms which either required prolonged incubation or did not grow on the primary isolation medium (CLED agar) were recorded as fastidious organisms and identified using standard or API technology. Organisms which grew only on the BaNal plates were recorded as anaerobes. For analysis of the results the volunteers were divided into the following age groups: 15 to 30 years (Group A); 31 to 45 years (Group B); 46 to 60 years (Group C).

Results

Results were available on 120 men: 36 in group A, 54 in group B and 30 in group C.

Of the 185 volunteers who were approached, 65 (35%) were unable to participate after reading the exclusion criteria. These comprised 35% of those aged between 15 and 30 years, 22% of those between 31 and 45 and 50% of those between 46 and 60. Microscopy showed minimal pyuria in 3 specimens (2.5%), 1 in each age group. None had a count > 10 cells/μl. Red cells were seen in 6 specimens (5%), 1 of which also showed pyuria; 5 specimens yielded only aerobic urethral commensals (*S. epidermidis* and *Enterococcus faecalis*) in mixed culture and counts $< 10^6$/l. These were disregarded as contaminants.

Table 1 shows the culture results and Table 2 lists the species of fastidious organisms isolated. No aerobes were isolated in pure culture. Fastidious organisms were isolated from 32 specimens from subjects throughout the age groups; the cultures were of a single species in 17 and mixed in 15. Some of these mixed cultures included anaerobes. The fastidious organisms were isolated in counts of 10^7/l in 8 specimens (7%) (*Gardnerella vaginalis* in 5); in the remaining 24 the counts were $< 10^7$/l.

Table 1 Culture Findings in MSUs from 120 Subjects

	Groups			
Culture	*A (%)*	*B (%)*	*C (%)*	*Total (%)*
No growth	23 (64)	38 (70)	21 (70)	82 (68)
Aerobes only	0 (0)	0 (0)	0 (0)	0 (0)
Anaerobes only	2 (5)	0 (0)	0 (0)	2 (2)
Mixed aerobes/anaerobes	0 (0)	0 (0)	2 (7)	2 (2)
Aerobes/mixed Gm + ve aerobes	0 (0)	2 (4)	0 (0)	2 (2)
Fastidious organisms (pure)	5 (14)	7 (13)	5 (16)	17 (14)
Fastidious organisms (mixed)	6 (17)	7 (13)	2 (7)	15 (12)
Total	36	54	30	120

Table 2 Identity of Fastidious Organisms

	Group			
Organism	*A*	*B*	*C*	*Total*
Gardnerella vaginalis	8	6	3	17
Fastidious streptococcus	1	3	1	5
Corynebacterium sp.	2	3	2	7
Lactobacillus sp	1	4	0	5
Not identified	0	0	2	2

Fastidious organisms were isolated from the 3 specimens which showed pyuria; 1 yielded *G. vaginalis* in pure culture (10^7/l) and the others yielded *Lactobacillus* sp. and *Corynebacterium* sp. in mixed culture ($< 10^7$/l).

Retraction of the foreskin made no obvious difference to the microscopic or culture findings. Of the 3 subjects with pyuria, 1 had retracted the foreskin; 65% of the 71 specimens in the first part of the study yielded sterile cultures, a figure similar to that of 73% of 49 specimens in the second part.

Discussion

The fact that 35% of possible volunteers were debarred by the exclusion criteria from taking part in the study confirms that urinary symptoms are commoner in males of all age groups than is generally believed. (The "recent antibiotic" clause is unlikely to have accounted for many exclusions in this sample of fit adult males).

The findings in respect of the isolation of Gram-negative aerobic pathogens are striking; no subject yielded pure growth of an aerobe in any count and only 2 yielded them in low counts ($< 10^7$/l) in mixed culture. This strongly supports the view that such organisms are not present as commensals in the lower urinary tract of the male.

Fastidious organisms were isolated from the specimens of 26% of the subjects, as pure culture in 14%. No counts of 10^8/l were recorded and only 8 (7%) were as high as 10^7/l. The species isolated most frequently was *Gardnerella vaginalis*; it is logical to assume that the presence of this and other fastidious species is probably the result of sexual transmission. The organisms which comprise the commensal flora of the distal urethra (*Enterococcus faecalis*, staphylococci) were not isolated from the specimens which yielded fastidious organisms. There are 2 possible explanations for this. Either the fastidious organisms had replaced the commensal aerobes in the distal urethra or they had become established at a higher level, possibly the proximal urethra, from which they might extend, under certain circumstances, to the prostate or bladder. There are well documented instances of bladder and upper tract infection with *G. vaginalis* in males (Abercrombie *et al.*, 1978; Finkelhor *et al.*, 1981; Wilson and Barratt, 1986; Fairley and Birch, 1989). This and other fastidious species have also been isolated from males with lower tract symptoms, possibly due to prostatitis (Lipsky and Plorde, 1985). It seems that, whilst their presence in the urethra may not give rise to symptoms, they may assume a pathogenic role by extension to the prostate or bladder. Differentiation between colonisation and infection might be made on clinical grounds, such as the presence of symptoms, and on laboratory findings, such as pyuria, bacterial count and purity of growth, in the same way that the significance of aerobic cultures is assessed.

Only 3 specimens (2.5%) showed minimal pyuria. We can conclude that urine from males who have not suffered from urinary symptoms does not contain white cells, and that their presence in clinical specimens is indicative of an inflammatory response to infection. It is interesting that of the 3 subjects with pyuria, all yielded fastidious organisms on culture, including a pure growth of *G. vaginalis* with a count of 10^7/l in one.

Lastly, retraction of the foreskin did not appear to make any difference to the microscopic or culture findings, suggesting that it is unnecessary to insist on this when MSUs are collected.

This study demonstrates, therefore, that Gram-negative aerobes isolated from clinical specimens from men, in whatever count, should be assumed to be significant and indicative of infection. At present the techniques for urine culture used in some laboratories are insensitive to counts as low as 10^6/l; in others, when such organisms are isolated in a count lower than 10^8/l, they are dismissed as contaminants and sometimes not reported. Clinicians who wish to make an accurate diagnosis and to be supplied with the appropriate antibacterial sensitivities should press laboratories on this point.

Secondly, we have shown that fastidious organisms are present in low counts in the urinary tract of a minority of men throughout the age groups. It is known that they have the potential to cause symptoms and an inflammatory response, and they were isolated from all 3 subjects with pyuria. We suggest that they should be sought by appropriate culture methods in specimens from male patients with either symptoms or pyuria which yield no aerobes on conventional culture. When this is undertaken in the laboratory very little pyuria is left unexplained (Clarke *et al.*, 1985); it is then reasonable practice to assume the possibility of chlamydial infection in men with pyuria in whom aerobic and fastidious organism culture is negative. Our practice is to recommend an empirical 2-week course of doxycycline for such patients. Only if the pyuria persists (and this occurs rarely) do we suggest culture of 3 early morning urine (EMU) specimens for *Mycobacterium tuberculosis*. Much time and effort is wasted in laboratories on this procedure because of a finding of apparently "sterile" pyuria;

this could be avoided if the protocol suggested here were followed.

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The Authors

I. D Sugarman, MB, ChB, Senior House Officer in Urology.

L. J Pead, AIMLS, Research Assistant, Public Health Laboratory

S R. Payne, MS, FRCS, formerly Senior Registrar in Urology. Now Consultant Urologist, Royal Infirmary, Manchester

R. M Maskell, DM, MRCP, Senior Medical Microbiologist, Public Health Laboratory

Requests for reprints to. R. M. Maskell, Public Health Laboratory, St Mary's Hospital, Milton Road, Portsmouth PO3 6AQ.

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Morbidity Following Cystoscopy: Comparison of Flexible and Rigid Techniques

S. W. DENHOLM, I. G. CONN, J. E. NEWSAM and G. D. CHISHOLM

University Department of Surgery/Urology, Western General Hospital, Edinburgh

Summary—Recent reports on the value of local anaesthetic flexible cystoscopy have emphasised excellent tolerance and preference for the technique over general anaesthetic rigid cystoscopy. However, no study has yet compared the post-operative morbidity rates of these procedures.

Tolerance, preference and post-operative symptoms in 100 patients undergoing local anaesthetic flexible cystoscopy were compared with those in 100 patients undergoing general anaesthetic rigid cystoscopy. On initial questioning, 89% of patients found flexible cystoscopy painless and 92% expressed a preference for the same procedure on a future occasion; 98 patients who underwent flexible cystoscopy and 87 who underwent rigid cystoscopy returned a questionnaire on symptoms 1 week after the procedure. The incidence of post-operative symptoms was 33% following flexible cystoscopy and 76% following rigid cystoscopy. Patients in both groups who were undergoing check cystoscopy had a lower incidence of morbidity than those undergoing cystoscopy for other reasons.

The results suggest that flexible cystoscopy was well tolerated and preferred by most patients. The morbidity associated with the procedure was also significantly less than that associated with rigid cystoscopy under general anaesthesia.

Flexible fibre-optic cysto-urethroscopy under local anaesthesia is established as a practical and economic alternative to traditional rigid cystoscopy under general anaesthesia (Clayman *et al.*, 1984; Fowler *et al.*, 1984; Webb *et al.*, 1984; Fowler, 1988). A recent report has revealed the excellent tolerance of the technique and the preference for local anaesthesia by the majority of patients (Flannigan *et al.*, 1988). However, no study has yet attempted to compare the incidence of minor post-operative morbidity following these procedures. When a flexible cystoscopy service was introduced in the Western General Hospital, Edinburgh, we took the oportunity of prospectively assessing tolerance, preference and post-operative morbidity in a series of out-patients attending for either local anaesthetic flexible cystoscopy or general anaesthetic rigid cystoscopy.

Patients and Methods

The first 100 consecutive out-patients undergoing flexible cystoscopy under local anaesthesia were studied (Group A) along with 100 consecutive out-patients undergoing rigid cystoscopy under general anaesthesia over the same time period (Group B). Randomisation was not performed and, during this initial evaluation period, selection for flexible cystoscopy was based on a low index of clinical suspicion of intravesical pathology. However, both groups were comparable because patients were excluded if any additional procedure such as urethral dilatation, biopsy or diathermy was performed during the examination.

Flexible cystoscopy was performed with an Olympus CYF flexible cystoscope using topical anaesthesia with 1% lignocaine gel. Rigid cystoscopy was performed under general anaesthesia using a 21F Storz cystoscope. Sterile water was used for irrigation in all cases. Patients who underwent flexible cystoscopy were questioned, immediately

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after the examination, on their tolerance of the procedure and preference for future examinations. All patients in both groups were given a questionnaire on symptoms and asked to complete and return it 1 week after the examination.

Results

Table 1 shows the characteristics of patients in each group. The average age was higher in Group A and more patients in this group underwent cystoscopy for follow-up of a bladder tumour. Rigid cystoscopy was performed more commonly for the assessment of obstructive or irritable bladder symptoms. Eleven patients who underwent flexible cystoscopy required further examination or treatment under general anaesthesia (Table 2); they included 3 patients with turbid urine in whom an adequate view of the bladder could not be obtained with the flexible scope.

All patients who underwent flexible cystoscopy answered the questionnaire immediately after the procedure; 89 found the procedure painless, 11 experienced pain or discomfort as the scope passed through the external urethral sphincter and 92 expressed a preference for the same technique on a future occasion rather than general anaesthetic rigid cystoscopy.

Ninety-eight patients in Group A returned the questionnaire after 1 week, compared with 87 in Group B (Table 3). The incidence of post-operative urinary syptoms was 33% in Group A and 76% in Group B. Eight patients in Group A (8%) and 26 patients in Group B (30%) complained of "feeling unwell" following their examination, with symptoms ranging from non-specific complaints of tiredness or general malaise to specific symptoms of back or testicular pain. Two patients (2%) in Group A and 9 (10%) in Group B attended their family doctor during the week following cystoscopy. In most cases (82%) an antibiotic was prescribed.

All patients who complained of any symptom post-operatively were included in an assessment of overall morbidity (Table 4). Males reported a higher incidence of symptoms than females, especially following flexible cystoscopy. Patients undergoing check cystoscopy reported significantly less morbidity than those undergoing cystoscopy for other reasons. In each subgroup, however, patients undergoing flexible cystoscopy had fewer symptoms than those undergoing rigid examination.

Preference for future cystoscopies was also obtained from the questionnaire returned after 1 week. Although on initial questioning, 92% in Group A said they would prefer a future examination under local anaesthesia, this fell to 85% of those who replied to the questionnaire 1 week later. Of the patients in Group B who replied to the questionnaire, 21% stated that they would prefer a future examination under local anaesthesia.

Table 1 Details of Patients

	Group A	*Group B*
Number	100	100
Males	50	56
Females	50	44
Average age (years)	57	58
Range	21–89	16–85
Indication		
Check cystoscopy	71	45
Haematuria	21	19
Outflow symptoms	2	14
Pain/bladder irritation	4	19
Other	2	3

Table 2 Pathology in Flexible Cystoscopy Group

Tumour recurrence	5
New tumour	2
Bladder stones	1
Severe cystitis/poor view	3
Total	11

Table 3 Replies to Questionnaire after 1 Week

	No of replies	
	Group A (%)	*Group B (%)*
Dysuria	21 (21)	51 (59)*
Frequency	14 (14)	36 (41)*
Haematuria	6 (6)	26 (30)*
Feeling unwell	8 (8)	26 (30)*
Consulted family doctor	2 (2)	9 (10)†
Total	98	87

* $P<0\cdot0001$ † $P<0\cdot02$ (Chi-square test)

Table 4 Overall Morbidity

	Group A (%)	*Group B (%)*
Total	33	76*
Male	42	78*
Female	24	74*
Checks	27	56†
Others	48	92*

* $P<0\cdot0001$ † $P=0\cdot002$ (Chi-square test)

Discussion

This study was not randomised and the 2 groups differed with respect to age and indication for cystoscopy. This was due to the selection for flexible cystoscopy, during initial evaluation of the technique, of older patients with a low risk of intravesical pathology (*e.g.* annual review check cystoscopies). This was reflected in the low incidence of pathology requiring a further general anaesthetic cystoscopy, compared with other reports of flexible cystoscopy (Webb *et al.*, 1984; Fowler, 1988). We feel, however, that despite these differences between the 2 groups, some valid conclusions can still be drawn from the results.

There was a high degree of acceptance and preference for local anaesthetic flexible cystoscopy. There was, however, a small group of patients who for various reasons found flexible cystoscopy an unpleasant, embarrassing or upsetting experience and who would have been better managed under general anaesthesia. This is a similar finding to that of Flannigan *et al.* (1988), who reported an 89% preference for local anaesthesia. In their study, however, the remaining 11% preferred a general anaesthetic procedure because of the associated overnight stay in hospital.

Almost all patients (98%) who underwent flexible cystoscopy returned the questionnaire compared with only 87% of those who underwent rigid cystoscopy. This may have been due to a greater degree of satisfaction in the former group. However, patients in the latter group were probably still drowsy when they were given the questionnaire and this may have contributed to the lower return rate.

The incidence of urinary symptoms was significantly lower following flexible cystoscopy. Although there were more patients undergoing check cystoscopy, which was shown in this study to be of lower morbidity, examination of subgroups showed that both check cystoscopies and cystoscopies for other reasons had lower post-operative morbidity rates when the flexible cystoscope was used. Possibly because of the easier instrumentation, the incidence of post-operative symptoms was lower in females than in males, especially following flexible cystoscopy.

Significantly more patients complained of "feeling unwell" after rigid cystoscopy and a greater percentage attended their doctor with post-operative symptoms. Some of these symptoms may, however, have been related to the general anaesthesia rather than to instrumentation.

Patients who underwent flexible cystoscopy were asked about their preference for future examinations on 2 occasions—once immediately after their cystoscopy and again in the postal questionnaire after 1 week. The preference for local anaesthesia fell slightly from 92% immediately after the procedure to 85% after 1 week. This may have reflected a "desire to please" by some patients when asked a question personally by the doctor but who subsequently answered more honestly in the postal questionnaire. Despite this, there was still a strong preference for the local anaesthetic procedure. Another interesting result was that 21% of the patients undergoing rigid cystoscopy stated a preference for local anaesthesia on a future occasion, though none had personal experience of local anaesthetic cystoscopy.

In summary, although the study groups were not totally matched, the results suggest that local anaesthetic flexible cystoscopy is well tolerated and is preferred by most patients. Assessment of symptoms during the week following their examination suggests that the morbidity of flexible cystoscopy is significantly less than the morbidity of rigid cystoscopy under general anaesthsia.

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The Authors

S W. Denholm, FRCS, Surgical Registrar.
I. G Conn, MD, FRCS, formerly Lecturer in Urology. Now Senior Registrar in Urology, St Woolos Hospital, Newport.
J E. Newsam, FRCS, Consultant Urological Surgeon
G D Chisholm, ChM, FRCS, FRCSE, Professor of Surgery and Honorary Consultant Urological Surgeon

Requests for reprints to· I G Conn, Department of Urology, St Woolos Hospital, Newport, Gwent NP9 4SZ.

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Effect of Capsaicin on the Rabbit Urinary Bladder. What is the Function of Sensory Nerves that Contain Substance P?

S. C. W. HARRISON, D. R. FERGUSON and M. R. HANLEY

Department of Urology, Addenbrooke's Hospital; Department of Pharmacology, University of Cambridge; MRC Molecular Neurobiology Unit, Cambridge

Summary—The sensory innervation of the rabbit urinary bladder was studied using local application of the specific sensory neurotoxin capsaicin (8-methyl-N-vanillyl-6-nonenamide). This agent has its major effect by damaging small diameter unmyelinated sensory nerves. The drug produced a 51% reduction in the bladder content of the neuropeptide substance P. It therefore appears that a substantial proportion of the bladder's content of the peptide is to be found in capsaicin-sensitive sensory nerves. Cystometrograms carried out before and after treatment with capsaicin were similar; this suggests that capsaicin-sensitive sensory nerves may not be of importance in the afferent limb of the micturition reflex. *In vitro* muscle strip studies demonstrated a small reduction in the sensitivity of the detrusor muscle to electrical stimulation of its intramural nerves. It is possible that *in vitro* intramural nerve stimulation leads to release of neurotransmitters from sensory as well as motor nerves. It is proposed that small diameter sensory nerves in the bladder wall may have a role in the transmission of the sensation of pain and in the triggering of inflammatory reactions rather than forming the afferent limb of the micturition reflex.

The innervation of the urinary bladder is complex and our understanding of the neural mechanisms remains incomplete. The excitatory and inhibitory nerve supply to the detrusor muscle can be studied in the organ bath but the sensory system is more difficult to examine. Lesioning experiments represent a classic approach to neurological study. Uemura *et al.* (1975) used surgical nerve section in their histological studies of the sensory innervation of the bladder, but selective lesioning requires dorsal root ablation over several spinal levels. An alternative approach is "chemical surgery", using sensory neurotoxins. This study is an example of this approach, using capsaicin to examine the role of the sensory innervation of the rabbit bladder.

Capsaicin has been shown to have highly selective effects on sensory nerves (Nagy, 1982; Buck and Burks, 1986). Administration to newborn animals causes irreversible degeneration and subsequent loss of primary sensory neurones (Jancsó *et al.*, 1977; Nagy *et al.*, 1981). Whether the drug causes neuronal death in adult animals is not yet clear but persistent impaired function in afferent fibres has been observed (Buck and Burks, 1986). Baranowski *et al.* (1986) applied capsaicin topically to the saphenous nerve of several species and demonstrated a block in nerve conduction particularly among the C fibre population. Gamse *et al.* (1982) found that application of the drug to the sciatic nerve led to reduced responses to noxious stimuli and also impaired axonal transport of substance P.

The effect of capsaicin on the rabbit bladder was examined in several ways. Urodynamic studies were used to assess the micturition reflex. Detrusor muscle function was studied using *in vitro* muscle strips. Finally, the effect of the drug on the substance P content of the bladder was examined in order to confirm that the agent had caused sensory nerve damage. Substance P is one of a number of peptides

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that have been shown to be present in pelvic nerve afferent fibres in the cat (De Groat *et al.*, 1986). It has not, however, been shown to be present in efferent nerves (Mattiasson *et al.*, 1985). The content of substance P in the bladder was measured by specific radioimmunoassay as in previous studies of the peptide in man and in experimental animals (Holzer *et al.*, 1982; Gu *et al.*, 1984).

Materials and Methods

Male New Zealand White rabbits weighing between 2 and 2.5 kg were used for the study. Urodynamic studies were performed prior to capsaicin or control treatments. Capsaicin was applied locally to the bladder in 5 rabbits and sham procedures were performed in 4. Six days after this procedure a repeat cystometrogram was undertaken. The following day the rabbit was killed and the bladder removed so that muscle strip studies and substance P assays could be performed.

Urodynamic studies were carried out on sedated animals; pentobarbitone sodium was administered via an ear vein at a dose that was titrated to the point where the animal would lie supine and not attempt to right itself (a dose of 30 mg was usually appropriate). The rabbit was catheterised with a 4 F infant feeding tube and placed in a pyrogen box which served to keep the animal still during the study. The box allowed sufficient room for the changes in posture that accompany voiding and had a slatted floor so that the voided urine did not wet the rabbit. The bladder was filled with 5-ml increments of normal saline at room temperature at 1-min intervals; intravesical pressure was monitored using a pressure transducer with the amplified signal being recorded on a chart recorder. The measurements included the volume required to give a rise in intravesical pressure of 5 cm H_2O (a value reflecting early filling compliance), the volume and pressure thresholds for micturition, peak voiding pressure and volume of residual urine. The filling/voiding cycle was repeated 2 or 3 times and the results averaged.

Capsaicin was administered with the animals under general anaesthesia. One rabbit received the drug by the intravesical route, 1 by infiltration of the pelvic plexus and 3 by both routes. A 1% solution of the drug in olive oil was used. For intravesical administration a 25-min instillation of 10 ml of the solution was used. For pelvic infiltration 0.3 ml of the solution was injected into the extraperitoneal plane around the bladder base; this was performed as an open procedure via a lower midline abdominal incision. The 4 control animals received olive oil alone, 1 by the intravesical route and 3 by combined bladder instillation and pelvic infiltration. Olive oil was selected as the capsaicin solvent because it has been shown to be without effect on nerve conduction when applied topically (Baranowski *et al.*, 1986).

Urodynamic studies were repeated on the sixth post-operative day and the following day the rabbits were killed by rapid intravenous injection of pentobarbitone sodium. The bladder was removed and urine sent for culture. The bladder was immersed in cold, oxygenated Krebs' solution, cleaned of extravesical tissue and subdivided into base, body and fundus. The base was defined as that part inferior to the attachment of the vasa deferentia, the fundus was the upper ⅓ and the base the lower ⅓ of the remaining segment. The anterior half of the bladder body was used for muscle strip studies and the remaining segments were frozen rapidly in liquid nitrogen for subsequent substance P assay.

In vitro muscle strip experiments were carried out on detrusor strips approximately 8 mm in length and 2 mm in diameter. They were stored for a maximum of 20 h at 4°C in oxygenated Krebs' solution. The strips were suspended in a 0.2 ml capacity superfusion chamber (Brading and Sibley, 1983) and superfused with Krebs' solution at 35°C at a rate of 1 ml/min. A loading tension of 0.5 g was applied and the strips allowed to equilibrate for 75 min before a 10-s control dose of carbachol (10^{-4} M) was administered. Isometric contractions were detected using a Grass FT03 tension transducer, amplified and recorded on a chart recorder. Experiments were carried out on muscle strips from each animal in the same sequence, 6 strips from each rabbit being used in total. Acetylcholine log dose response curves were constructed by the administration of 10-s doses of the drug in the range 10^{-7} to 10^{-2} M. Nerve-mediated responses were examined using electrical field stimulation to construct frequency response curves (5-s trains of 50-V square wave pulses with a 50-μs pulse width at stimulation frequencies in the range 2.5–50 Hz). Stimulation parameters were chosen to stimulate selectively intramural nerves present in the muscle strips rather than detrusor muscle fibres themselves. This was confirmed by the finding that contractions resulting from stimulation could be inhibited using tetrodotoxin (3×10^{-7} M). The inhibitory effect of a β-adrenergic stimulation on detrusor contractions was examined by producing log dose response curves to isoprenaline. Increasing concentrations of isoprenaline were added to the superfusate in the dose range 10^{-8} to 10^{-5} M. A standard stimulus was applied at each dose level in the form of a 10-s application of carbachol at a dose that produced a contraction that was 75% of the maximum response to cholinergic stimulation. In addition, a standard nerve-mediated contraction was applied at each dose level by stimulation using the standard parameters at 40 Hz. Finally, the sensitivity of the detrusor muscle to direct electrical stimulation was examined. Voltage response curves were constructed in the presence of tetrodotoxin (3×10^{-7} M) using single 100-ms stimuli in the voltage range 10 to 140 V; the tetrodotoxin served to block depolarisation of the intramural nerves so that contractions were the result of depolarisation of the smooth muscle cells.

The measurement of substance P in the bladders was undertaken by radioimmunoassay (Too, 1985; Harrison, 1988). Tissue extraction was carried out following the thawing of the frozen bladder sections using a method based on that described by Too (1985). The bladder segments were weighed and finely chopped before 2 ml of 0.1 M boiling acetic acid was added and the tissue incubated for 10 min in a boiling water bath. The samples were homogenised, centrifuged and aliquots of the supernatant separated and freeze dried. The resulting extracts were stored at −20°C until assayed. The specific antibody used for the assay was rabbit α 140 which is directed against the N terminal fragment of substance P and is specific for this tachykinin (Lee *et al.*, 1980; Too, 1985). The antibody was used at a final concentration of 1 in 40,000 with a ^{125}I Bolton and Hunter substance P tracer (Amersham). Incubations of antibody, tracer and tissue extract were carried out at pH 7.5 for 48 h at 4°C. A standard curve was constructed using known concentrations of substance P. Separation of the antibody/peptide complex was achieved by precipitation with cold absolute alcohol and centrifugation. The radioactivity in the resulting pellet was measured using a γ counter.

Statistical analysis of the urodynamic data and substance P assay results were carried out using the *t* test. The analysis of the response curves obtained from the muscle strip experiments was initially by computer curve fitting using a Hill equation. The resulting computer estimates of the EC_{50} (the stimulus required to produce a contraction which is 50% of the maximal response) and maximal response for the 2 groups of rabbits were compared using the *t* test. The Hill equation did not prove to be a suitable model for analysing the frequency response experiments. Analysis of this data was undertaken using a linear transformation programme to compare the 2 curves (Harrison, 1988).

Drugs were obtained from Sigma Chemicals unless otherwise stated.

Results

No complications were seen as a result of the surgical procedures. Bladder contractions were not observed during administration of the capsaicin. In the post-operative period all of the rabbits appeared to eat, drink and void normally with no retention of urine.

The results of the pre- and post-operative cystometrograms of the capsaicin-treated animals showed no significant differences (Table). The control group also showed no significant differences in the results of the urodynamic studies.

One rabbit from each group had a significant growth of *Staphylococcus aureus* in the urine, the remaining samples being sterile.

All of the bladders appeared macroscopically normal and the mean weights were similar for both groups. The response of the strips to a near-maximal, control dose of carbachol was not significantly different when compared using the *t* test ($P > 0.05$); mean tension (± standard error of the mean) for the capsaicin group was 1.81 (±0.15) g (n = 30) and for the control group 2.31 (±0.22) g (n = 24). The acetylcholine log dose response curves for the 2 groups did not differ significantly (Fig. 1). Nerve-mediated responses did, however, differ between the 2 groups. The maximum response to electrical field stimulation, expressed as a percentage of the maximal contraction obtained using acetylcholine, was not significantly different; the mean for the capsaicin group (±S.E.M.) was 43.9%

Table Urodynamic Data: Capsaicin-treated Rabbits

	Pre-operative (n=5)	*Post-operative (n=5)*
Volume at 5 cm H_2O pressure (ml)	35.4 (±3.9)	32.0 (±3.4)
Volume threshold for micturition (ml)	43.8 (±5.4)	39.6 (±7.0)
Pressure threshold (cm H_2O)	11.7 (±0.9)	12.5 (±1.3)
Peak voicing pressure (cm H_2O)	16.6 (±1.2)	16.4 (±1.9)
Residual urine (ml)	19.6 (3.6)	13.6 (±3.5)

Values are means (± standard errors of the mean) There were no significant differences in any of the parameters measured (i.e. $P > 0.05$)

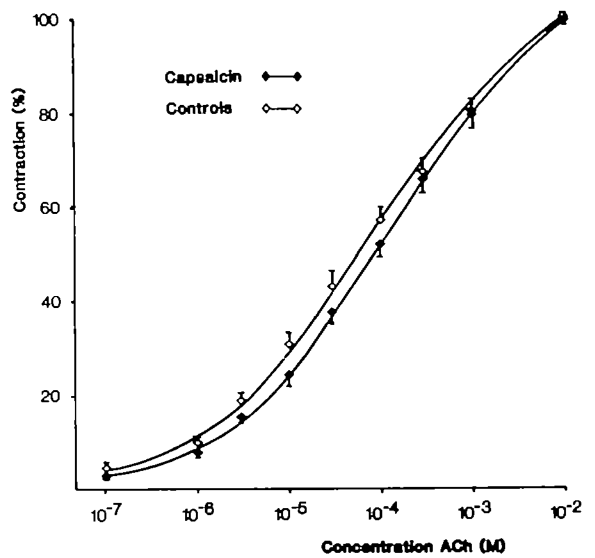

Fig. 1 Acetylcholine log dose response curves for muscle strips from capsaicin-treated (n=20) and control (n=16) rabbits. Contractions are expressed as a percentage of the maximum response obtained during the experiment Values are means ± S E M The computer-generated best fit curves are shown, EC_{50} values for the 2 groups did not differ significantly.

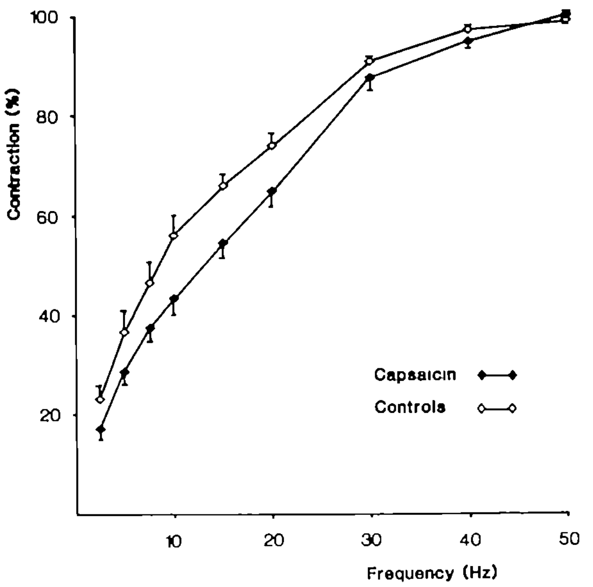

Fig. 2 Frequency response curves for muscle strips from capsaicin-treated (n=20) and control (n=16) rabbits. Contractions are expressed as a percentage of the maximum response obtained during the experiment. Values are means ± S.E.M Linear transformation analysis showed the curves to differ significantly.

(±3.8%) and for the controls 43.1% (±4.2%). However, the frequency response curve for the capsaicin group was found to lie to the right of that for the controls (Fig. 2); this shift was found to be significant using the linear transformation analysis ($P<0.01$). The muscle strips from capsaicin-treated rabbits therefore appear to be less sensitive to intramural nerve stimulation than control strips. The inhibitory effect of isoprenaline proved to be similar for the 2 groups regardless of whether the stimulus was carbachol or field stimulation. Computer-estimated values for maximal inhibition and IC_{50} for the 2 groups did not differ in either experiment. Log dose response curves using carbachol stimulation are shown in Figure 3. The voltage response curves for the 2 groups did not differ significantly (Fig. 4).

Capsaicin treatment resulted in an approximately 50% reduction in the total bladder content of substance P. Mean total substance P content (± S.E.M.) for the capsaicin group was 2.05 (±0.24) × 10^{-12} moles and for controls 4.02 (±0.45) × 10^{-12} moles. This difference was significant ($P=0.02$). Similar falls in the content of substance P were found in the different regions of the bladder (Fig. 5).

Discussion

Administration of capsaicin to the rabbit bladder led to a depletion of half of the substance P content without alteration in the urodynamic function of the bladder. It therefore appears that, although a substantial proportion of the bladder's substance P is to be found in sensory nerves, the depletion was limited, leaving the question open as to why this reduction was not greater. A possible explanation is that the method of drug administration did not lead to exposure of all of the sensory nerves. For example, infiltration of phenol into the pelvic floor of the rabbit gives only partial bladder denervation (Harrison, 1988). Use of the additional intravesical route should have increased exposure of nerves to the drug since capsaicin has been shown to penetrate the bladder mucosa (Santicioli *et al.*, 1985) and the connective sheath surrounding nerves (Baranowski *et al.*, 1986). The timing of the assay following capsaicin administration may be another factor affecting peptide depletion. Gamse *et al.* (1982) showed that substance P depletion was maximal 1 week after exposure to the drug in the rat. This time course may be different in the rabbit or there may be a greater recovery in this species. A third explanation as to why substance P depletion was incomplete is that the rabbit may be less sensitive to capsaicin than other species, such as the rat and guinea-pig (Gamse *et al.*, 1982; Baranowski *et al.*, 1986). A fourth possibility is that the residual peptide is present in sensory nerves that are capsaicin-resistant or in another population of neurones. In the rat, however, using neonatal systemic administration, depletion is not complete. Holzer *et al.* (1982) obtained at most an 84% reduction in this way. Therefore some bladder substance P may be present in capsaicin-resistant sites. In keeping with this, multiple populations of sensory nerves innervating the urinary bladder have been proposed to have varying degrees of capsaicin sensitivity (Maggi and Meli, 1988). The possibility that substance P might be an excitatory motor transmitter in the rabbit bladder has been ruled out in earlier work (Husted *et al.*, 1981).

The present study did not reveal any changes in capsaicin-treated animals in the sensitivity of detrusor muscle strips to acetylcholine, isoprenaline or direct electrical smooth muscle stimulation. Furthermore, the maximal response to intramural nerve stimulation did not differ between the 2 groups of rabbits. However, capsaicin treatment produced decreased sensitivity to electrical field stimulation of the intrinsic nerves. Since capsaicin is selective for sensory nerves (Buck and Burks, 1986) and has no effect on field stimulation responses in the rat (Sharkey *et al.*, 1983), this finding was unexpected. The possibility that some non-specific motor nerve damage may have occurred is unlikely, since denervation experiments using phenol rendered rabbit muscle strips supersensitive to acetylcholine (Harrison, 1988) whereas such a change was not observed in the present experiments. It is possible that the change in sensitivity was due to a reduction in substance P release from sensory nerves in the muscle strip preparation. Matusǎc and Bauer (1986) concluded that the reduced nerve-mediated responses of guinea-pig ileum seen after capsaicin desensitisation were caused by reduced transmitter release from sensory nerves. Electrical field stimulation is a non-physiological response whose result will depend on activity in all components of the innervation of the tissue being studied. Maggi *et al.* (1986) suggested that release of substance P from sensory nerves in the rat might cause an increase in myogenic contractile activity.

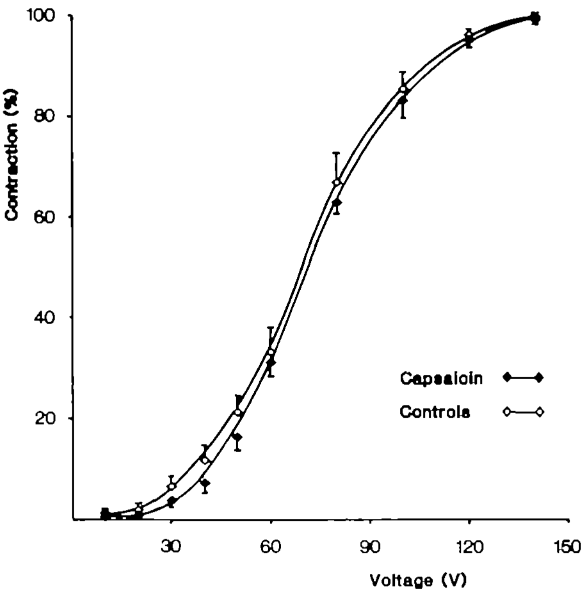

Fig. 4 Voltage response curves for muscle strips from capsaicin-treated (n = 10) and control (n = 8) rabbits Contractions are expressed as a percentage of the maximum response elicited during the experiment Values are means ± S E M. The computer-generated best fit curves are shown, the curves do not differ significantly

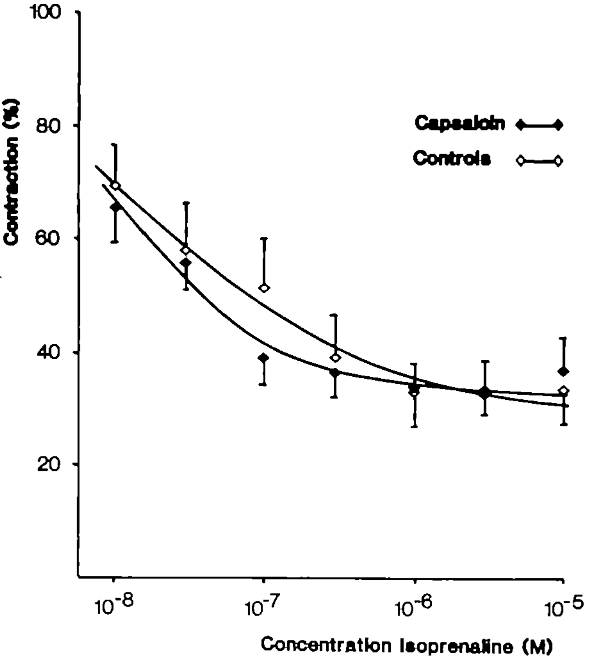

Fig. 3 Isoprenaline log dose response curves for muscle strips from capsaicin-treated (n = 10) and control (n = 8) rabbits Contractions were elicited in response to electrical stimulation of the intramural nerves and are expressed as a percentage of the response obtained in the absence of isoprenaline. Values are means ± S E M The computer-generated best fit curves are shown; the curves do not differ significantly

No alteration in the function of the micturition

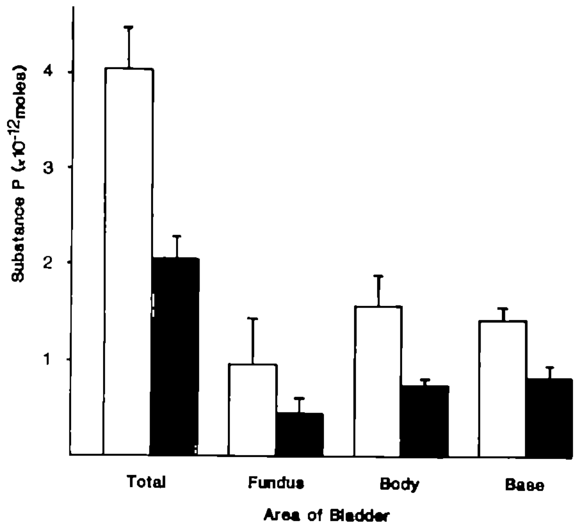

Fig. 5 Substance P content of bladders treated with capsaicin (n=5, shaded bars) and control bladders (n=4, white bars). Values are means ± S E M. Significant reductions in substance P content are seen in all areas of the bladder except the fundus.

reflex was detected in response to capsaicin treatment since the results of urodynamic studies were similar before and after application of the drug. This finding contrasts with those from previous studies carried out in the rat and guinea-pig (Sharkey *et al.*, 1983; Holzer-Petsche and Lembeck, 1984; Maggi *et al.*, 1984, 1987). In the rat, capsaicin leads to retention of urine due to loss of the sensory limb of the micturition reflex. Maggi *et al.* (1986) concluded that capsaicin-sensitive sensory nerves convey information regarding bladder volume but felt that the adult rat had some capsaicin-resistant fibres so that voiding could occur at increased volumes; the function of the substance P found in the peripheral terminals of some sensory nerves was thought to be regulation of detrusor and vascular tone. Why then was no change observed in the function of the rabbit bladder? It is possible that peptide depletion and sensory nerve function are independent in this species, so that sensory nerves functioned normally despite substance P being depleted from the bladder. Alternatively, the lower sensitivity of the rabbit to capsaicin may have led to insufficient disturbance in afferent nerve function to cause an alteration in overall function. A more important possibility is that capsaicin-sensitive sensory nerves do not form part of the micturition reflex in this species. Although not entirely specific, capsaicin has its major effect on small unmyelinated C fibres (Nagy *et al.*, 1981; Buck and Burks, 1986). However, in the cat, De Groat *et al.* (1981) presented evidence that the afferent limb of the micturition reflex is composed of A fibres. The same might prove to be true in the rabbit.

If capsaicin-sensitive sensory nerves are not components in the micturition reflex, what function might these nerves serve? In other systems such nerves are involved in the transmission of information regarding noxious stimuli (Jancsó *et al.*, 1977; Buck and Burks, 1986). It is possible that this population of nerves in the rabbit bladder serves a similar function. Furthermore, the release of substance P from peripheral terminals may act as a trigger for inflammatory reactions. The release of the peptide from peripheral nerve endings has been shown to cause vasodilatation and plasma extravasation (Lembeck and Holzer, 1979). Saria *et al.* (1983) and Maggi *et al.* (1987) demonstrated that substance P can cause plasma extravasation in the rat and guinea-pig bladder. The involvement of bladder sensory nerves in initiating inflammatory reactions is an area which merits further research. It has been noted that some patients develop frequency and dysuria after ingesting foodstuffs which have a peppery flavour (Charlton, 1985); it is possible that capsaicin, or similar compounds, in the pepper are triggering acute inflammatory episodes. In the clinical context, it is interesting to speculate whether capsaicin-like drugs may prove to be of value. Extrapolation from the rabbit suggests that such drugs may be found to be useful in the desensitisation of the bladder in inflammatory disorders rather than in the control of the overactive micturition reflex.

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The Authors

S C. W. Harrison, MA, MChir, FRCS, formerly Research Registrar in Urology, Addenbrooke's Hospital Now Senior Registrar in Urology, Southmead Hospital, Bristol.

D R. Ferguson, MD, Lecturer, Department of Pharmacology.

M R Hanley, PhD, Senior Staff Scientist, MRC Molecular Biology Unit.

Requests for reprints to S C W Harrison, Department of Urology, Southmead Hospital, Westbury-on-Trym, Bristol BS19 5NB.

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A New Device for Self-catheterisation in Wheelchair-bound Women

GILLIAN M. HUNT and R. H. WHITAKER

Department of Urology, Addenbrooke's Hospital, Cambridge

Summary—The Deavin-Hunt device is designed to help paraplegic and incontinent women to catheterise themselves whilst in a wheelchair. Such patients with neuropathic bladder might otherwise be unable to use intermittent catheterisation, an effective method of controlling incontinence and preserving the kidneys.

Intermittent self-catheterisation (ISC) can be highly successful in controlling urinary incontinence and preventing renal damage (Diokno *et al.*, 1983). However, ISC may not be easy for a female in a wheelchair if she is paraplegic from injury or disease such as myelomeningocele or multiple sclerosis. These conditions may be associated with pain, instability or deformity of the spine, adductor spasm, loss of sensibility in the perineum and poor manipulation (Hunt *et al.*, 1984). With the help of members of the orthopaedic staff we designed a simple device to enable such patients to catheterise themselves in a wheelchair.

Patients and Methods

The Deavin-Hunt device* consists of two U-shaped aluminium leg pieces connected by adjustable bars and supporting a mirror (Fig.). The rods are attached by a swivel joint to the leg pieces and are held together by a double tubular joint. The joint, which is held by 2 wing nuts, allows separation of the leg pieces from 4 to 18 cm. The legs are secured by webbing which is held by a plastic hook and easily adjustable buckle. The aluminium leg pieces, which are padded with plastozote, can be bent slightly to conform to the width of the thigh. The detachable and adjustable mirror is secured to the tubular joint by a rod 15 cm in length. Further adjustment of the direction of the mirror rod relative to the legs can be obtained by releasing the 2 wing nuts on the tubular joint. The device can easily be cleaned and the padding and fastening replaced as necessary. It can be taken apart at the tubular joint so that it will fit into a handbag or a small box 25 × 17 × 5 cm. It weighs 340 g.

Eight severely disabled wheelchair-bound patients evaluated the device and advised modifications. They suffered from myelomeningocele (3), multiple sclerosis (2), spinal tumour, transverse myelitis and paraplegia of unknown cause.

Discussion

The main difficulties were achieving the best position for catheterisation, finding the urethral orifice and catching the urine as it left the catheter. The patient had to sit as near to the front edge of the wheelchair seat as possible and to lean well back. By supporting the feet on the steps of the wheelchair, or higher on a stool or chair, the patient was balanced in a semi-reclining position and the pelvis conveniently tilted. Balance and stability were crucial to those patients with a high paraplegia and one patient preferred to use a safety belt. Adductor spasm was overcome by adjusting the width of the device. When sitting on the front edge

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* The Deavin-Hunt Catheterisation Device costs £57 plus VAT (1989 price). It is manufactured and marketed by Cumbria Orthopaedic Ltd, Surgical and Orthopaedic appliance manufacturers, Unit 25, Chaucer Industrial Park, Watery Lane, Kemsing, Sevenoaks TN15 6PL.

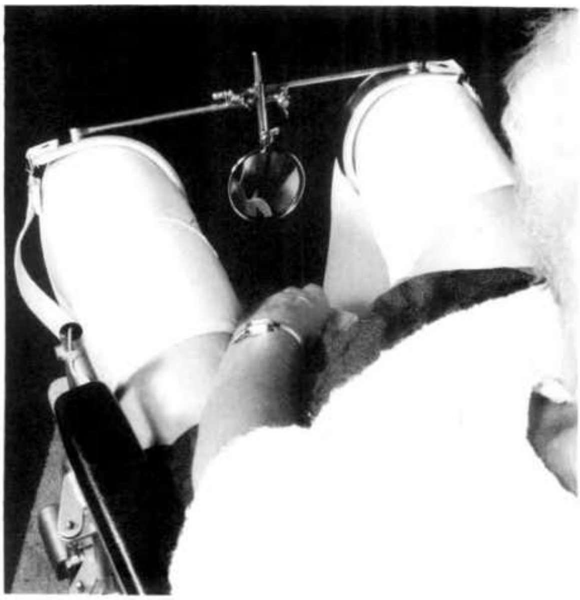

Fig. The Deavin-Hunt device.

of the wheelchair the thighs were no longer supported by the seat and the soft tissues of the thighs dropped away instead of obstructing the view of the perineum (Fig.). The mirror afforded an excellent view and the wheelchair could be rotated to make use of available lighting. Some patients catheterised by feel alone. Patients had less difficulty catching the urine if they attached a leg bag to the catheter or used a longer male catheter directed into a container fastened to the wheelchair. The device could also be used on the lavatory with the patient sitting as far *back* as possible on the seat, or directly on the porcelain. Thus the mirror could hang down within the lavatory bowl, allowing space for manipulation of the catheter. The Deavin-Hunt device is also useful whilst patients are learning the technique of ISC as it enables them to see the urethral orifice.

This simple device can bring the social and medical advantages of ISC within the reach of paraplegic women, thereby freeing them from some of the restrictions imposed by the combination of a wheelchair existence and urinary incontinence.

Acknowledgements

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The Authors

Gillian M. Hunt, MB, DCH, Clinical Assistant.
R. H. Whitaker, MD, MChir, FRCS, Consultant Urologist.

Requests for reprints to: G. M. Hunt, Department of Urology, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ.

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Trans-trigonal Phenol Failed the Test of Time

T. P. ROSENBAUM, P. J. R. SHAW and P. H. L. WORTH

Institute of Urology and St Peter's Hospital, London

Summary—The results following 94 trans-trigonal phenol injections in 60 patients over a 5-year period are analysed. In only 1 patient was there a lasting effect. The others all required alternative treatment for bladder instability, hyper-reflexia or hypersensitivity. Older patients with normal bladder compliance and patients with a neuropathic aetiology had slightly better results but also failed to derive lasting benefit. The complications associated with the treatment and the general anaesthetic outweigh the transient benefits of this technique.

The treatment of patients with bladder instability, hyper-reflexia and hypersensitivity continues to be a challenge for urologists. Since we do not yet fully understand the precise mechanism of these abnormalities, treatment has been aimed at controlling symptoms.

In 1982 Ewing *et al.* described the technique of subtrigonal phenol injection for the treatment of urge incontinence in females with detrusor instability. This appeared to offer an interesting alternative treatment and in a group of 30 female patients the overall response rate was 62.5% at 1 year. In 1984 Blackford *et al.* described their experience with this technique in 116 female patients; they reported a success rate of 51% in all patients and 69% in older patients with detrusor instability at 1 year.

The present study reviews the long-term results of using this technique in 60 patients with urodynamically proven detrusor instability, hyper-reflexia or hypersensitivity at St Peter's Hospitals, London.

Patients and Methods

From July 1983 to October 1988, 60 patients were treated by trans-trigonal phenol injection of the nerves of the pelvic plexus. This therapy was adopted when more conservative measures had failed. All patients had been urodynamically assessed prior to treatment and were confirmed to be unstable, hyper-reflexic or hypersensitive. There were 56 female and 4 male patients. The latter were treated after the risk of impotence was explained and accepted. The mean age was 50.4 years (range 21–80).

Patients were followed up 1, 2, 3, 6, 12 and 24 months after the procedure and assessed clinically. Relapse usually developed gradually and was considered to have occurred when recurrent symptoms were severe enough to warrant further treatment.

Patients were injected between 1 and 5 times (mean 1.6) (Table 1); 94 separate treatments were given and the length of the response after each treatment was assessed by reviewing the case histories.

Technique

The technique has been described by Ewing *et al.* (1982) and involved the injection of a 6% aqueous solution of phenol using a 20 gauge metal Shuttleworth needle (length 45 cm) introduced through a cystoscope fitted with an Albarran deflecting mechanism. In 75 cases (80%) the amount injected was 5 to 10 ml and the site was halfway between the ureteric orifice and the internal urethral meatus on each side. In 19 cases (20%) the technique varied slightly because of personal preference or technical difficulty. In some cases 3 or 4 injections were needed to reach the pelvic plexus nerves but the

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Read at the 45th Annual Meeting of the British Association of Urological Surgeons in St Helier, June 1989

Table 1 Number of Phenol Injections/Patient

No. of injections	*No. of patients*
1	37
2	16
3	4
4	2
5	1

total amount injected never exceeded 20 ml. Precise location was assisted in the female patients by *per vaginam* palpation of the tip of the needle. A Foley catheter was left *in situ* for 24 h and patients were usually discharged on the following day.

Urodynamic evaluation

All patients had 1 or more urodynamic assessments prior to treatment. The 4 male patients had bladder instability and the filling pattern showed reduced compliance. Twelve female patients had sensory problems (8 had sensory urgency and 4 had bladder pain); 18 had phasic instability only and 16 had reduced compliance. In 10 unstable female patients the case notes did not describe the filling pattern and the tracings could not be re-examined.

Results

The amount of phenol injected and the number and the site of the injections (Table 2) did not appear to have a significant influence on the results of treatment.

In all male patients the results after 1 treatment were disappointing and second treatments were not attempted (Table 3). These patients were excluded from further analysis in order to have a series comparable to others previously published.

In female patients the overall success rate at 1 month was 48%; at 6 months it was 16% and at 1 year it was 3%. One female patient who was unstable following pelvic surgery was rendered acontractile by the phenol injection and remained so 2 years later. All of the other patients either failed to respond or their symptoms recurred and they were offered alternative treatment.

Urodynamic groups

The best results were obtained in patients with bladder instability where the filling pattern showed phasic contractions with normal compliance (mean response 2.7 months). In patients with low compliance the mean response was 1.6 months. In both groups the results appeared better in patients over the age of 50. In the 10 unstable patients whose filling pattern had not been recorded the mean response was 2.3 months, an intermediate value. The worst results were obtained in patients with sensory urgency (mean 1.6 months). Only 4 patients were treated for bladder pain and their mean response was 2 months. None of these differences was statistically significant (Table 4).

Aetiological groups

Female patients were divided into 3 groups according to the aetiology of their bladder abnormality: (1) after pelvic surgery, (2) neuropathic, (3) idiopathic (Table 5).

A detailed analysis of the results is shown in Table 6.

Table 2 Amount, Site and Results of Phenol Injections

Amount/Site	*No. of injections*	*Failed (%)*	*1/12 (%)*	*6/12 (%)*	*24/12 (%)*	*Not known*
10 ml/R&L	36	20 (56)	16 (44)	6 (17)	1 (3)	0
5 ml/R&L	39	16 (41)	18 (46)	3 (8)	0	5
Others	19	10 (53)	9 (47)	2 (11)	0	0
Total	94	46 (49)	43 (46)	11 (12)	1 (1)	5

Table 3 Results in Male Patients

Age	*Aetiology*	*No. of injections*	*Result*	*Results*
79	Idiopathic	1	Failed	Suprapubic catheter
50	Multiple sclerosis	1	Failed	Indwelling catheter
61	Unstable after transvesical prostatectomy	1	Failed	Ileocystoplasty
63	Primary	1	Failed	Unchanged

Table 4 Results in Female Patients (According to Urodynamic Group)

Urodynamic group	*Age (years)*	*No. of patients*	*No of injections*	*Duration of response (months)*
Bladder pain		4	6	2.00
Sensory urgency		8	10	1.55
Unstable phasic		18	31	2.70
	<50	11	20	2 11
	>50	7	11	3.70
Unstable low compliance		16	30	1.63
	<50	7	11	1 09
	>50	9	19	1.95
Unstable undetermined		10	13	2.30

Table 5 Abnormalities in Female Patients

Group	*No. of patients*
After pelvic surgery (n = 26)	
Hysterectomy	12
Marshall Marchetti operation	1
Marshall Marchetti + hysterectomy	1
Multiple gynaecological operations	6
After childbirth	4
Abdominoperinal resection	1
Bladder neck repair	1
Neuropathic (n = 16)	
Multiple sclerosis	3
Parkinson's disease	1
DM	1
Polio	1
Myasthenia gravis	1
Spina bifida + cord lipoma	1
RTA (road traffic accident) cervical spine injury	1
RTA · lower spinal injury	1
RTA : head and pelvic injuries	1
Friedreich's ataxia	1
Spinal fusion for spondylolisthesis	1
Delayed myelinisation	1
Recurrent meningioma	1
Cavernous angioma of fourth ventricle + X-ray therapy	1
Idiopathic (n = 14)	
Primary	5
Secondary	9

Failure to obtain any benefit after treatment was greatest in the idiopathic group (61%), followed by the pelvic surgery group (47%) and then the neuropathic group (33%). The same pattern was observed at successive out-patient assessments. Neuropathic patients had the highest success rate (59% at 1 month and 22% at 6 months) followed by pelvic surgery patients (50% at 1 month and 15% at 6 months). The worst results occurred in idiopathic patients (30% at 1 month and 9% at 6 months). Two neuropathic patients had a lasting effect at 1 year (7%) but by 2 years had relapsed. All idiopathic patients had relapsed at 1 year and one pelvic surgery patient remained acontractile at 2 years (Cox and Worth, 1986). Five patients were either lost to follow-up or no data were available (Fig. 1).

Each aetiological group was divided into 2 subgroups, those below and those above 50 years of age. There was no age difference between the neuropathic and pelvic surgery patients. The younger subgroup of idiopathic patients had slightly better early results but this difference disappeared after follow-up at 3-months (Figs 2–4).

Neuropathic patients with a urodynamic filling pattern showing phasic contractions and normal compliance had a mean response of 2 months; this represented no improvement on the group of all patients with the same filling pattern.

There was no evidence that a second or subsequent injection altered the success rate.

Complications

Two patients had post-operative haematuria which required prolonged catheterisation and hospitalisation, but no blood transfusion was needed. One patient developed chronic retention and still has a non-contractile bladder 2 years after treatment (Cox and Worth, 1986). There was no record of ureteric reflux, major nerve plasy or damage to the bladder wall.

Discussion

The treatment of severe bladder instability, hyperreflexia and hypersensitivity presents a challenge

Table 6 Results in Female Patients (According to Aetiological Group)

		Continued improvement at						
Group	*Failed (%)*	*1/12 (%)*	*2/12 (%)*	*3/12 (%)*	*6/12 (%)*	*12/12 (%)*	*24/12 (%)*	*Not known (%)*
After pelvic surgery (n=40)	19 (47)	20 (50)	13 (32)	9 (22)	6 (15)	1 (3)	1 (3)	1 (3)
Neuropathic (n=27)	9 (33)	16 (59)	14 (52)	12 (44)	6 (22)	2 (7)	0 (0)	2 (7)
Idiopathic (n=23)	14 (61)	7 (30)	6 (26)	5 (22)	2 (9)	0 (0)	0 (0)	2 (9)

to urologists. We do not yet fully understand the precise nature of the defect that causes these abnormalities (Mundy, 1988). The balance between the afferent and efferent autonomic supply to the bladder and sphincter mechanism appears to be altered and recent work suggests a change in 2 different types of sensors, an early warning sensor and a stretch sensor, that are present in the bladder and in the trigone (Klein, 1988). The result is a patient whose ability to control micturition is reduced. Treatment has been aimed primarily at restoring the function of the bladder as a reservoir. Anticholinergic medication helps in a number of mild cases. When this fails, many bladder denervation procedures have been used (Torrens and Hald, 1979). These include sacral rhizotomy (To-

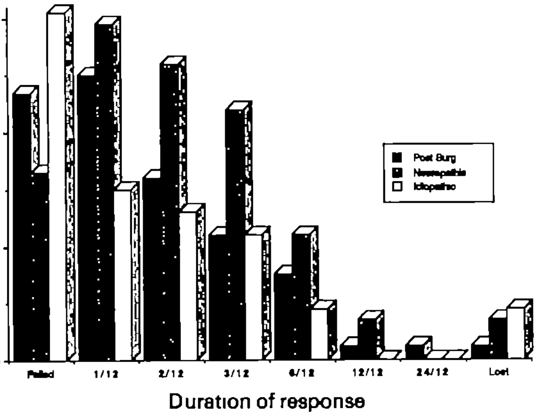

Fig. 1 All aetiological groups.

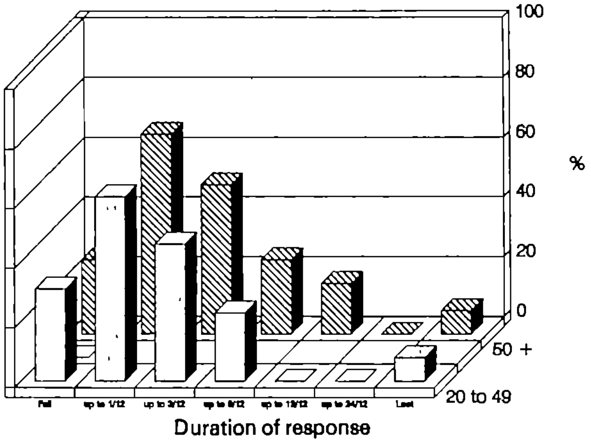

Fig. 3 Neuropathic group according to age.

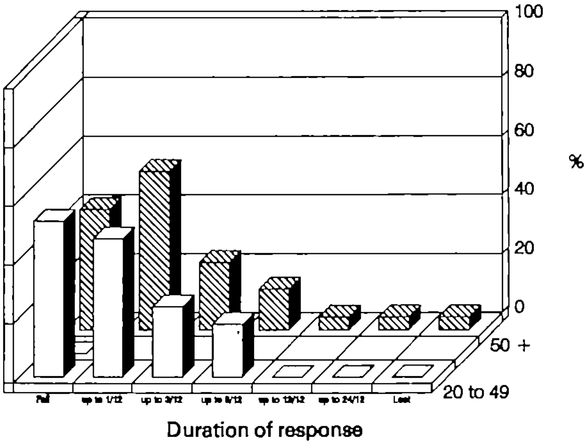

Fig. 2 Pelvic surgery according to age.

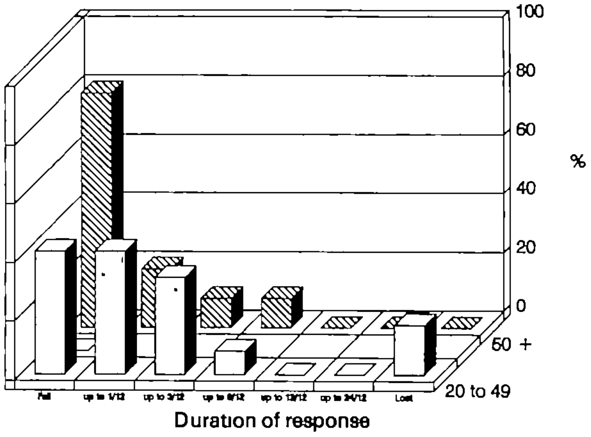

Fig. 4 Idiopathic group according to age

czek *et al.*, 1975), sacral neurectomy (Marshall, 1954), selective sacral neurectomy (Torrens and Griffith, 1974), hydrostatic bladder distension (Dunn *et al.*, 1974), supratrigonal denervation of the bladder (Essenhigh and Yeates, 1973; Gibbon *et al.*, 1973), transvaginal denervation (Ingelman-Sundberg, 1975) and endoscopic bladder transection (Parsons *et al.*, 1984). Some of these procedures are still used, although the beneficial effects are debatable.

Our results show that clinical denervation after trans-trigonal phenol injection of the pelvic plexus nerves with a 6% aqueous solution of phenol is at best only transient. In only 1 patient was there a lasting effect at 2 years and she was unusual in that she had had many pelvic operations in the past. In 47% of cases the injection had no effect at all and in only 16% did the effect last for 6 months or more (Table 6).

Using a urodynamic classification, the best mean response of 2.7 months was found in patients with a filling pattern of phasic instability, and in this group it was better in the older patients (3.7 months). In the low compliance group, although the overall results were poorer, there was a better response in older patients (Table 4).

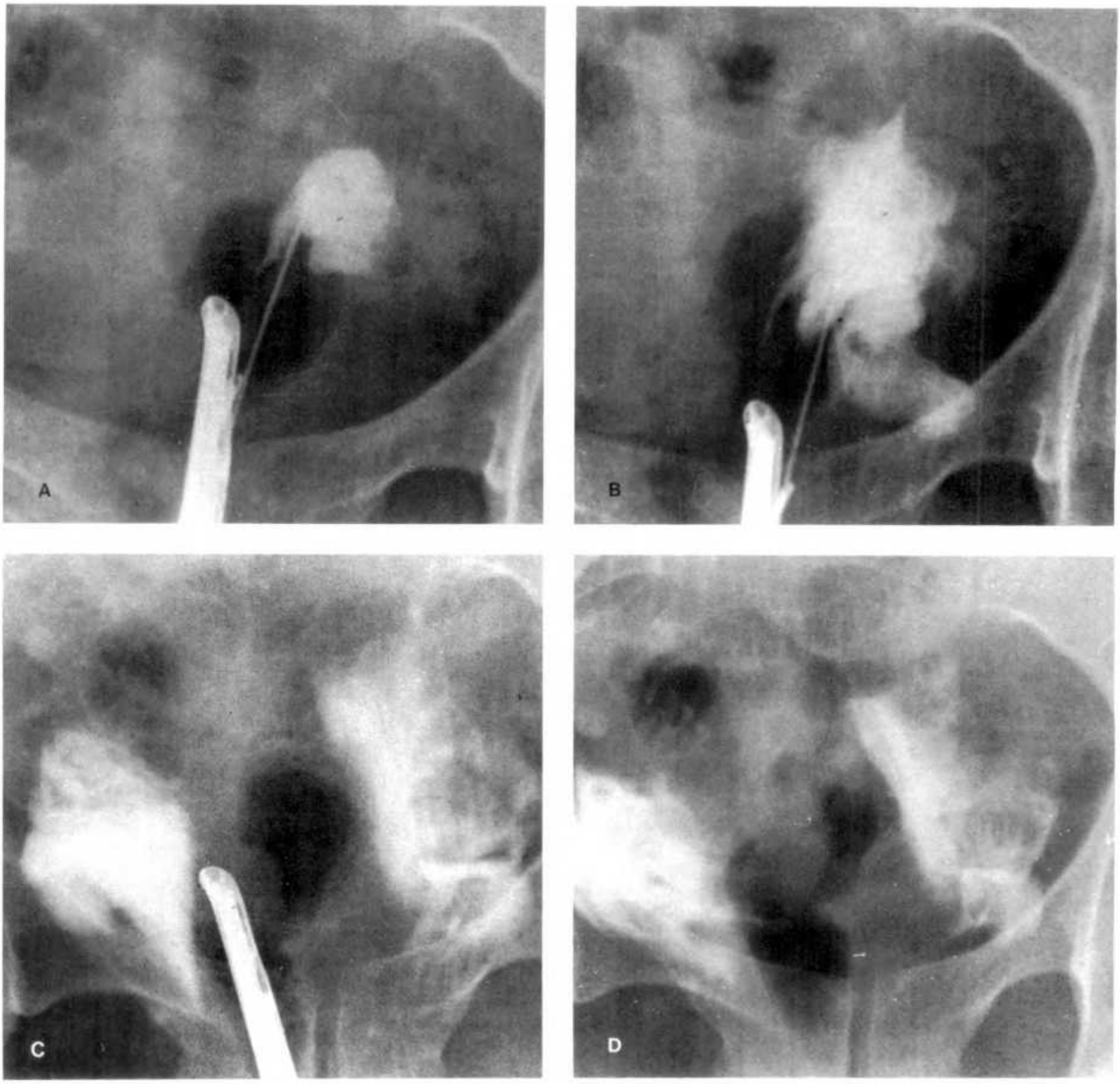

Fig. 5 Diffusion of phenol injection at 30 s, left (A), 2 min, left (B), 8 min, left; 2 min, right (C), 17 min, left; 11 min, right (D).

When the results were analysed (grouping the patients according to their primary pathology and age) there was little difference between the pelvic surgery group (Fig. 2) and the idiopathic group (Fig. 4), all age groups being equally unsuccessful. However, there was a trend towards better results in the neuropathic group (Fig. 3), these being slightly more sustained in the older age group. Nevertheless, most of these patients had relapsed by 6 months. This difference in age groups has also been reported by Blackford *et al.* (1984), but the long-term results were disappointing. In our idiopathic patients the younger subgroup had slightly better early results but this difference disappeared after 3 months. The relatively few complications in our series included 1 patient with chronic urinary retention and 2 with bleeding. Ureteric reflux, sloughing, stricture and fibrosis of the lower ureter, bladder fistula, femoral nerve palsy and accidental eye damage to the surgeon have been reported by Cameron-Strange and Millard (1988) and Chapple *et al.* (1989). To these should be added the risks of the general anaesthetic.

These findings lead us to conclude that the use of trans-trigonal phenol in its present form for the treatment of bladder instability and hypersensitivity cannot be justified. It may still have a place in the treatment of neuropathic patients with bladder hyper-reflexia, particularly to control "by-passing" in catheterised patients with multiple sclerosis and in the occasional patient who is prepared to accept the temporary nature of the relief. Older patients with normal compliance may have a slightly longer response.

One reason for the poor results and complications may be that the phenol diffuses widely through the extravesical fat (Fig. 5) and the concentration of phenol may quickly become suboptimal in the area of the pelvic plexus nerves. Parkhouse Fitzmaurice *et al.* (1987) compared the nerve damage caused by various concentrations of phenol in solution with water, glycerine and oil when injected into the rectovesical pouch of rats. They found a significant reduction in the autonomic nerve density of the bladder after the injection of 2.5 and 5% phenol in aqueous solution as well as 2.5% phenol in glycerine solution. No significant effect was found using 5% phenol in oil. They suggested that a lower concentration of phenol in water or glycerine might reduce the incidence of side effects.

Perhaps we should now explore other ways, both chemical and physical, to obtain a more permanent bladder denervation. Many centres now use the clam enterocystoplasty to treat patients when more conservative measures have failed (Bramble, 1982; Mundy, 1988).

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The Authors

T. P Rosenbaum, FRCSE, Clinical Lecturer
P J. R Shaw, FRCS, Senior Lecturer, and Honorary Consultant Urologist
P. H L Worth, FRCS, Consultant Urologist

Requests for reprints to: T P. Rosenbaum, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE

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Protease and Plasminogen Activator Activity in Human Bladder Carcinoma

U. GORELIK, A. LINDNER and M. MAYER

Department of Urology, Wolfsohn Hospital, Holon; Department of Biochemistry, Hadassah University Hospital, Jerusalem, Israel

Summary—The ability of human bladder tissue extracts to cleave ^{14}C-labelled globin in the absence and in the presence of plasminogen was assayed to quantify non-specific protease and plasminogen activator (PA) activity, respectively. In normal human bladder tissue the non-specific protease activity was approximately 2-fold higher than in tissue samples obtained from transitional cell carcinoma of the bladder (TCC). In contrast, PA activity was almost 4-fold higher in TCC than in normal transition cell epithelium. Acid-treated urine from 19 patients with TCC of the bladder exhibited significantly higher levels of plasminogen activator activity than similarly treated urine from controls. These results indicate that malignant transformation of the bladder epithelial tissue results in elevated levels of PA in the tissue and in urine. Further studies are needed to assess the potential of PA determination in the management of bladder cancer patients.

The serine protease plasminogen activator (PA) converts the abundant circulating zymogen plasminogen into the broad spectrum active protease plasmin (Collen, 1980). The plasmin degrades fibrin clots, extracellular-matrix proteins and also activates more molecules of plasminogen (Dano *et al.*, 1985). It thus amplifies the limited proteolysis initiated by PA to an extent required for fibrinolysis or for degradation and remodelling of tissues (Reich, 1978; Dano *et al.*, 1985). PAs are widely distributed in mammalian organs and PA-mediated extracellular proteolysis is implicated in processes such as thrombolysis, tissue involution and cell migration (Astrup, 1978; Reich, 1978; Collen, 1980; Dano *et al.*, 1985, 1988).

An association has also been noted between increased cellular synthesis of PAs and malignancy, and many studies have shown that PA is increasingly expressed in the malignant phenotype (Collen, 1980; Dano *et al.*, 1988).

Both normal human bladder cells and transformed human bladder cells in culture produce fibrinolytic activity (Tympanidis and Astrup, 1971; Hisazumi *et al.*, 1973; Pearlstein *et al.*, 1976). Since a major component of the fibrinolytic activity is plasminogen activation, it is not surprising that production of PA and PA inhibitors was observed in normal and cancerous bladder cells (Hisazumi and Fukushima, 1973; Pearlstein *et al.*, 1976; Hisazumi *et al.*, 1977; Nagy *et al.*, 1977; Wilson *et al.*, 1980).

It was also reported that PA activity characteristic of normal rat bladder epithelium gradually decreased following the induction of bladder transitional cell carcinoma with oral administration of N-butyl-n-butanol (4)-nitrosamine. The reduction was associated with increased levels of urokinase inhibitor activity (Hisazumi and Fukushima, 1973).

This report draws attention to an increased level of PA in TCC of the human bladder compared with normal human bladder mucosa. A similar difference is also reflected in urinary PA activity in these groups.

Materials and Methods

Tissues and urine samples

Tissue sections were obtained from TCC of the bladder by a transurethral incision with biopsy

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forceps. Only superficial, non-invasive, low grade tumours (stage O) were taken for analysis. Control tissue sections were taken from tumour-free, apparently normal mucosa. Control bladder and prostate samples were also obtained from patients undergoing surgery for benign prostatic hypertrophy (BPH). Mucosa tissue was separated from the outer-facing tissue by the submucosal injection of normal saline prior to incision. Prostatic tissue was taken after suprapubic prostatectomy from the central section of a lobe chosen at random and cut in the middle. All tissue samples were thoroughly rinsed in cold 0.01 M phosphate buffered saline (PBS), pH 7.4, and kept at −20° until further processing.

Tissue extracts were obtained from the samples after thawing, 3 washes in PBS and homogenisation of 40 to 100 mg tissue in 0.2 ml PBS using an ultraturax homogeniser for 20 s. The homogenate was sonicated in a Branson Sonifier by 3 cycles of 20 s each. During and between sonification cycles the homogenate was kept in an ice-water mixture.

Triton x-100 to a final concentration of 0.25% was added and the samples were mixed and centrifuged for 10 min at 3000 rpm in a refrigerated Sorvall centrifuge. The supernatant was taken for protease and PA assays (see below) and also for protein determination (Pesce and Strande, 1973).

Measurement of tissue protease and PA activity

The non-specific protease activity was measured by the degradation of [^{14}C]-labelled globin (17 mg protein/ml; 2–6 × 10^5 cpm/mg protein) prepared as described previously (Lernau *et al.*, 1980). Incubation was for 3 h at 37° in a shaking water bath. The reaction was terminated with 250 μl of ice-cold 50% (vol/vol) trichloroacetic acid. The tubes were cooled to 4°, centrifuged at 5000 × g for 25 min, and 400 μl of the acid-soluble supernatant fraction was taken for scintillation counting in 4.5 ml of Lumax scintillator.

PA was determined by the same procedure, except that 10 μl of plasminogen (8 mg/ml) were added to the reaction mixture and the plasminogen-dependent increase in globinolytic activity (above the activity obtained in the absence of plasminogen) was measured. Earlier studies have established that the plasminogen-dependent globinolytic activity measured by this method reflects PA activity (Finci *et al.*, 1986). Results are given in μg of globin degraded by 1 mg of protein during 3 h. The variation coefficients (CV) are typically below 5% (within-run) or 8% (between-run).

Urinary protease and PA activity were measured in a similar way on 0.4 ml of urine, following acidification to abolish acid-sensitive protease inhibitory activity. Acidification consisted of incubation of the urine samples for 10 min with one-tenth volume of 0.1 M glycine-HCl buffer, pH 2.0, containing 1% gelatin; the pH was readjusted adding one-tenth volume of 2.0 M tris-HCl buffer, pH 7.8. Urinary creatinine was determined by the picric acid method (Murray *et al.*, 1987).

Fibrin monomers

Those were obtained by treating fibrinogen with thrombin. Thrombin, 1 u/ml, was added to 2 mg/ml of fibrinogen in PBS. The mixture was incubated at 37°C for 10 min. The clot was squeezed by rolling it on a glass rod and by compression against the tube wall, quickly washed twice in PBS and dissolved in 1.2% acetic acid to a final concentration of 2 mg/ml.

Results

TCC samples were obtained from 9 patients by direct biopsy of the tumour; 28 samples of normal bladder mucosa were obtained either from apparently normal areas of the bladder in the same individuals or from bladders of patients undergoing surgery for benign prostatic hypertrophy. Table 1 shows the mean values of PA activity obtained in these samples, indicating a significantly ($P < 0.001$) higher mean activity of the fibrinolytic enzyme in TCC than in control bladders. In 3 patients, samples were removed from the tumour and from a normal section of the same bladder. Comparison of their PA levels showed that the tumour had 2.6-6.1- and 9-fold higher PA activity than the normal mucosa. Taken together with the results of the pooled cases showing a 4-fold difference (Table 1),

Table 1 PA Activity in Bladder and Prostate Samples

Tissue	*PA activity* *μg globin/mg protein* *mean ± SEM*
Normal bladder*	303 ± 45 (n = 28)
Bladder tumour†	1212 ± 144‡ (n = 9)
Benign prostatic hypertrophy	172 ± 58 (n = 14)

Plasminogen activator activity was assayed by following the plasminogen-dependent cleavage of ^{14}C-labelled globin. The tissue samples were homogenised and sonicated, and activity of PA determined in the supernatant fraction as detailed in Methods

*Tissue obtained from apparently normal areas of the bladder in tumour-bearing patients, or from the normal bladder of patients undergoing surgery for benign prostatic hypertrophy

†Biopsy taken directly from the tumour tissue. Only stage O tumours were taken for analysis

‡Significantly different from normal bladder values ($P < 0.001$).

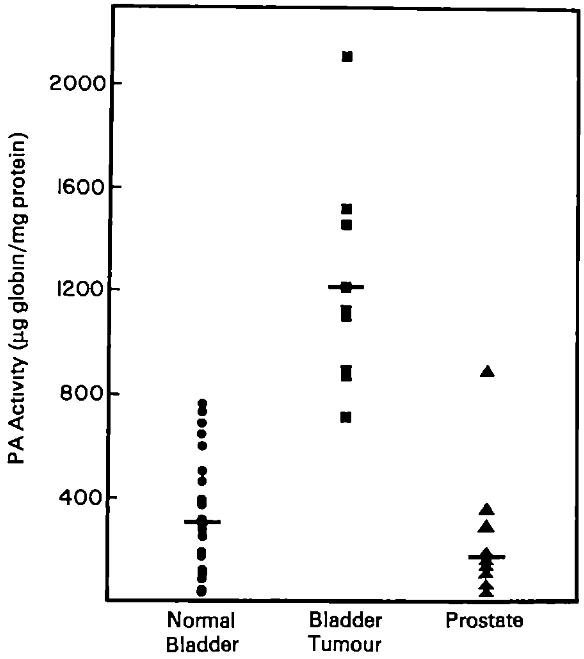

Fig. PA activity in tissue samples obtained from normal bladder, tumour and normal prostate tissue. See Materials and Methods for experimental details.

these findings indicate that bladder neoplasia is associated with stimulation of PA activity. No significant differences were noted between tumours assessed as grade I, II or III. The distribution of the individual results is further depicted in the Figure.

Table 1 also shows the PA activity of prostatic tissue, amounting to about 56% of that measured in bladder mucosa. During the course of this study, no tissue samples were available from patients with prostate cancer, so that a comparison of PA activity in normal versus cancerous prostate was not feasible.

In 1 case it was possible to sample the PA activity in the same individual on 2 different occasions. First, during surgery a sample of TCC displayed PA activity of 774 μg/mg protein. The same patient was operated on again 3 months later because of recurrence. At the second sampling, PA activity of 1083 μg globin/mg protein was observed. These values should be compared with the mean PA level of non-TCC controls amounting to 303 μg globin/mg protein (Table 1).

Table 2 shows the non-specific proteolytic activity of the tissue extracts, measured by following the ability of the extracts to degrade ^{14}C-globin in the absence of exogenous plasminogen (Milwidsky *et al.*, 1985; Finci *et al.*, 1986). Under these conditions the globinolytic activity reflected general protease activity exclusive of PA, since the substrate of PA was excluded from the reaction mixture. The results showed that the non-specific proteolysis was almost 2-fold higher in non-TCC cases than in TCC.

Urinary PA-like activity can be assayed by the same globinolytic assay in which the plasminogen-dependent increment in globinolysis is followed. However, due to presence of PA inhibitors in urine, prior acid treatment of the urine is instrumental in abolishing the activity of inhibitors. Following this acidification, the urine of patients with TCC of the bladder showed only a 50% higher level of mean PA activity than the mean PA activity of non-TCC cases (Table 3). This increase was statistically significant ($P<0.05$). However, a comparison of PA activity in the non-TCC controls classified by diagnosis indicated that the apparently lower level in non-TCC cases was probably misleading. This was mainly due to the inclusion of 3 patients with spermatic vein ligation showing very high urinary PA, and 10 patients with kidney stones whose high urinary PA approached that of the TCC samples. Only the 6 cases of stress incontinence had markedly lower PA activity. The low levels in the latter group were apparently responsible for the reduced mean level of PA in the pooled results of non-TCC cases (Table 3).

Discussion

Using a double-stage functional reaction of the plasminogen-dependent globinolytic activity as a highly sensitive assay of PA, an association was found between TCC of the bladder and increased production of PA. Increased rates of plasminogen activation due to PA derived from the tumour tissue could therefore contribute to the facilitated fibrin-

Table 2 Non-specific Protease Activity in Bladder and Prostate Samples

Tissue	*Proteolytic activity μg globin/mg protein, mean ± SEM*
Normal bladder	426 ± 60 (n = 21)
Bladder tumour	272 ± 45* (n = 18)
Benign prostatic hypertrophy	432 ± 104 (n = 15)

Cleavage of ^{14}C-globin by the supernatant fraction of tissue homogenates was determined in the absence of exogenous plasminogen Preparation of the homogenates and assay conditions were as in Table 1, except for the absence of plasminogen

*Significantly different from normal bladder values ($P<0.05$).

Table 3 Urinary PA Activity

Source of urine	*PA activity cpm/µmol creatinine*
TCC (n = 19)	19,303 ± 3,387
Non-TCC (all controls, n = 19)	13,094 ± 2,208*
Subdivision of controls	
Kidney stone (n = 10)	17,030 ± 2,553
SVL (n = 3)	26,877 ± 2,299†
Stress incontinence (n = 6)	6,459 ± 637‡

Urine samples from a 24-h collection were acid treated to remove PA inhibitory activity and assayed for their plasminogen-dependent globinolytic activity

*Significantly different from TCC cases ($P < 0.05$)

†Significantly different from TCC cases ($P < 0.01$).

‡Significantly different from TCC cases ($P < 0.005$)

olytic activity encountered in patients with TCC. The present results on tissue samples studied *in vitro* for their ability to produce PA are in accordance with earlier findings on tissue cultures that indicated tumour cells as strong producers of PA (Pearlstein *et al.*, 1976; Hisazumi *et al.*, 1977; Kinjo *et al.*, 1979; Wilson *et al.*, 1980; Dano *et al.*, 1985). In contrast to the general observation that tumours produce more PA than their normal counterparts, Hisazumi *et al.* (1973, 1974) and Hisazumi and Fukushima (1973) reported that transformation to malignancy stimulated production of a urokinase inhibitor and a consequent reduction in fibrinolysis. They were unable to find any difference between the fibrinolytic activity produced by normal bladder epithelial tissue and that produced by bladder cancer, probably as a result of a high inhibitory content in the 2 cell types (Hisazumi *et al.*, 1973). Evaluation of the changes in level and/or activity of the various inhibitors of PA by means of specific antibodies and specific inhibition assays are expected to clarify this situation. Indeed, the reciprocal relationship between general proteolytic activity and PA activity in the bladder samples (compare Tables 1 and 2) might be a result of the presence of potent inhibitors of PA and/or non-specific protease activity. The inhibitor(s) would modulate the activity and produce the reciprocal activity noted in normal bladder transition epithelium versus TCC of the bladder. Incidently, normal bladder cells were shown earlier to produce and to secrete cathepsin B1, a non-specific protease that is expected to exhibit globinolytic activity in the absence of plasminogen (Pietras *et al.*, 1975).

An inhibitor likely to play a role in these processes is plasminogen activator inhibitor type-1, recently shown to be induced in culture by tumour promoters (Mayer *et al.*, 1988).

With immunochemical methods the plasminogen-dependent globinolytic activity can be defined as being due to urokinase or tissue-type plasminogen activator (Astrup, 1978; Reich, 1978; Dano *et al.*, 1985, 1988). It is possible that the pattern of production of the different types of PA is a characteristic response of the cells, and that normal and cancer cells produce distinct patterns of these 2 enzymes (Dano *et al.*, 1988). This contention is supported by our finding (not shown) that fibrin monomers enhance urinary PA activity with a greater effect in urine from TCC cases than in control urine from non-TCC cases. Thus the addition of 20 µg of fibrin monomers to urine samples led to a 63% stimulation of PA in urine from TCC patients and only a 23% increase in samples from non-TCC cases. Since fibrin monomers are known preferentially to stimulate tissue-type PA (Verheijen *et al.*, 1982), a larger percentage of PA in TCC samples appears to be a tissue-type like enzyme. It is not known whether neoplastic transformation is reflected by a change in the relative amounts of urokinase and tissue-type PA produced by the cells (Dano *et al.*, 1985).

Components of the PA system were recently shown to be involved in the formation and/or disruption of cell-cell and cell-substratum contacts (Dano *et al.*, 1989). Since tumour growth and cell migration depend on cell adhesion and cell-matrix interaction, it is possible that PA activity in bladder tumours is stimulated to promote these processes during neoplastic transformation.

These observations on urinary PA activity, based on results normalised for urine creatinine content, show considerable variability. Nevertheless, a significant difference is noted between the high levels of PA in tumour-bearing patients and the low enzyme content of controls free of tumour. When the non-TCC patients are subdivided into groups by specific diagnoses, a clear difference is discernible. the highest enzyme levels are present in individuals with kidney stones and the lowest levels in stress incontinence (Table 3).

Both TCC and inflammatiaon provoke PA activity. Since the neoplastic process is often associated with secondary inflammation, it is possible that inflammation is in part responsible for the overall change in tumour PA activity. The relative contribution of the neoplastic process *per se* and associated or secondary processes, such as inflammation, to the changes noted in PA production remain unclear.

Determination of PA levels in prostatic tissue reveals that the hypertrophic prostate contains general protease and PA-like protease activity of a magnitude similar to the respective activity in normal prostate tissue. Samples from prostatic cancer tissue were not available and therefore a comparison between hypertrophic and neoplastic tissue was not feasible.

In conclusion, the association between enhanced PA levels and TCC could be used to evaluate patients. Provided that the enhancement in PA is both sensitive and specific for TCC (and that it proves to be a reliable method) assays of PA activity in bladder biopsies and eventually in urine could assist in the management of patients with TCC.

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The Authors

U Gorelik, MD, Senior Urologist, Wolfsohn Hospital

A. Lindner, MD, Chief, Department of Urology, Wolfsohn Hospital

M. Mayer, DSc, Professor of Human Biochemistry and Head, Department of Biochemistry, Hadassah Medical Center.

Requests for reprints to. M. Mayer, Department of Clinical Biochemistry, Hadassah Medical Center, P.O. Box 12000, il-91120, Jerusalem, Israel.

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Prevalence of Urinary Symptoms in Men Aged over 60

J. P. BRITTON, A. C. DOWELL and P. WHELAN

Departments of Urology and General Practice, St James's University Hospital, Leeds

Summary—The prevalence of urological symptoms in elderly males in the community is poorly documented. A series of 578 men, aged 60 to 85 years and registered with one inner city health centre, completed a self-administered questionnaire which enquired about current urological symptoms. Many symptoms were common, including a lengthening of the time to pass urine (26%), a deterioration in urinary flow (30%), dribbling (26%), urgency (31%), increased day-time frequency (32%) and nocturia (57%); 102 men (18%) gave 5 or more positive responses to the 13 questions relating to urological symptoms. In contrast, during a 2-year period, only 17 men, aged 60 to 85 years, were referred to a urology department from the same health centre. The implications of these findings are discussed.

In men, urinary symptoms become increasingly common with age. The prevalence of urinary incontinence in elderly males ranges from 6 to 19% (Feneley *et al.*, 1979; Thomas *et al.*, 1980; Diokno *et al.*, 1986) but other equally troublesome symptoms, such as urgency, frequency and nocturia, may be present in up to 50% (Milne *et al.*, 1972).

We have investigated the prevalence of urinary symptoms in a group of elderly men registered with one inner city health centre, and compared this with the referral pattern to a urological department.

Patients and Methods

A total of 855 men, aged 60 to 85 years, were invited to attend a health screening clinic during 1988. Those considered unfit to attend because of terminal disease, severe immobility or dementia were excluded. The 578 men (68%) who did attend were asked to complete a self-administered questionnaire which had previously been validated in a combined hospital/general practice study; it included questions about past urological history and current urological symptoms.

Details of hospital referrals for the 2-year period from January 1987 to December 1988 were obtained from health centre records.

Results

The prevalence of urinary symptoms is shown in Table 1. Many symptoms were common and nearly all showed an increased prevalence with age, although only urgency and nocturia reached statistical significance. The number of urological symptoms reported by each patient is shown in Table 2;

Table 1 Prevalence of Urological Symptoms in 578 Males

	No of men (%)	
	Age (years) 60–69 330 (100%)	*Age (years) 70–85 248 (100%)*
Difficulty passing urine	8(2)	12(5)
Longer to pass urine	80(24)	68(27)
Slowing of urinary stream	93(28)	83(33)
Sit down to pass urine	10(3)	9(4)
Strain to pass urine	7(2)	6(2)
Dribbling incontinence	83(25)	69(28)
Urgency	88(27)	92(37) $P<0.01$
Increased daytime frequency	100(30)	84(34)
Nocturia × 1	172(52)	158(64) $P<0.005$
Nocturia × 2 or more	73(22)	73(29)
Nocturnal incontinence	2(1)	5(2)
Recent or past dysuria	17(5)	8(3)
Recent loin pain	7(2)	5(2)
Total	330	248

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Table 2 Urological Symptoms

No of symptoms	0	1	2	3	4	5	6	7	8	9	10
No of patients	126	109	100	81	60	42	31	15	10	2	2
(%)	(22)	(19)	(17)	(14)	(10)	(7)	(5)	(3)	(2)	(1)	

102 patients (18%) gave 5 or more positive responses to the 13 questions.

Some patients had previously been told by a doctor that they had "bladder trouble" (6%), urine infection (8%) or "prostate trouble" (11%); 40 patients (7%) had previously undergone prostatectomy (9 in the 60–69 year group, 31 in the 70–85 year group). The mean age at prostatectomy was 67 years (range 49–80).

In the 2-year period from January 1987 to December 1988, 17 men over the age of 60 years were referred to a urology department, a referral rate of less than 1% per annum. The mean age at time of referral was 73 years (range 61–80; 15 patients were referred with a provisional diagnosis of "prostatism", 1 with recurrent urinary tract infections and 1 with frequency and nocturia.

Discussion

The results of this study showed that urinary symptoms were common in a group of relatively active men, aged 60 to 85 years, taken from an inner city community. All symptoms became more common with increasing age, particularly nocturia and urgency; others included frequency, dribbling and a slowing of the urinary stream, with 18% of patients admitting to 5 or more symptoms.

Urinary incontinence, probably the most embarrassing symptom, has been reported in up to 18% of men over the age of 60 (Feneley *et al.*, 1979; Thomas *et al.*, 1980; Diokno *et al.*, 1986). We found a prevalence of 27%, although we used its most liberal definition, asking patients if "they ever dribble into their pants". For many patients such incontinence may be inconsequential, but for others this distressing condition requires treatment.

Analysis of hospital referrals revealed that less than 1% of men over the age of 60 years were referred to a urology department each year.

The disquieting message is that the urologist sees only a small fraction of the total problem and many more patients may be in need of further assessment and treatment.

Some men may not find their symptoms troublesome and adapt their lifestyle accordingly and in some cases the symptoms may be transitory. Others may regard their symptoms as "part of the process of ageing" and thus not abnormal. Whether we should redefine "normal" for this group or whether we are failing to treat symptoms which would be amenable to medical or surgical therapy remains unknown. Further research is needed to investigate the clinical significance of these symptoms.

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The Authors

J P. Britton, FRCS, Tutor and Honorary Registrar, Department of Urology.

A. C. Dowell, MRCGP, Lecturer, Department of General Practice

P. Whelan, MS, FRCS, Consultant Urologist

Requests for reprints to: J. P. Britton, Department of Urology, Guy's Hospital, St Thomas Street, London SE1 9RT

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Does Microinvasion of the Capsule and/or Micrometastases in Regional Lymph Nodes Influence Disease-free Survival after Radical Prostatectomy?

F. HERING, M. RIST, J. ROTH, M. MIHATSCH and G. RUTISHAUSER

Urological Clinic, Department of Surgery, University Hospital, Basle, Switzerland

Summary—Since 1976, 126 patients with clinically localised carcinoma of the prostate have been managed by radical retropubic prostatectomy. All patients with tumour spread beyond the capsule or metastasis in lymph nodes received radiotherapy. Tumour category pT3 was divided into invasion of the capsule or infiltration of the seminal vesicle.

The disease-free 10-year survival rate in patients with minimal invasion of the capsule was 72% and in patients with infiltration of the seminal vesicles it was 26%. Unilateral lymph node metastases were classified as microscopic disease or macroscopic infiltration.

The disease-free 10-year survival rate in patients with metastasis in 1 lymph node (micro- and macro-metastasis) was 65% in contrast to 0% in patients with bilateral disease.

Radical prostatectomy has become established as a proper form of treatment for localised prostatic cancer. The 10-year overall survival rate is approximately 80% for categories pT1 and pT2 (Schroeder and Belt, 1975; Gibbons *et al.*, 1979; Elder *et al.*, 1982). If the disease extends beyond the borders of the prostate, or if the tumour spreads into the lymphatic system, the prognosis of patients who undergo surgery is adversely affected (Boxer *et al.*, 1971; Jewett *et al.*, 1975; Gervasi *et al.*, 1985; Middleton *et al.*, 1986; Paulson *et al.*, 1986). In spite of the introduction of sophisticated imaging techniques, understaging still occurs in approximately 50% of cases (Jewett, 1975; Catalona *et al.*, 1982; Middleton and Smith, 1982; Pontes *et al.*, 1985). The effect of minimal tumour invasion of the prostatic capsule and of microscopic metastasis in a unilateral lymph node remains unclear. The aim of this study was to investigate any adverse effects on disease-free survival and on overall survival rates in these categories compared with T2N0 categories.

Patients and Methods

All patients undergoing surgical treatment for localised carcinoma of the prostate in this unit since 1976 were followed up in a prospective study.

After bilateral staging lymphadenectomy, radical retropubic prostatectomy was performed.

Clinical staging included rectal examination by at least 2 clinicians, chest X-ray and urography, bone scan, urethrocystoscopy, computed tomography of the pelvis and abdomen (bipedal lymphangiography up to 1980) and evaluation of serum alkaline and acid phosphatase levels, (supplemented since 1984 by determination of PSA).

In most cases fine needle aspiration biopsy was used to confirm the diagnosis; in the remaining cases core biopsies were used for histology. Clinical stages were assigned according to the tumour, nodes and metastasis system (UICC, 1987). Patients with histologically confirmed tumour spread beyond the capsule or metastases in regional lymph nodes received adjuvant radiotherapy.

From 1976 to October 1987, 126 patients were treated by radical prostatectomy and 117 of them were evaluable. Their mean age was 63.7 years

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(range 45–76). Follow-up ranged from 5 months to 11 years (median 3 years 4 months) and consisted of physical examination with chest X-rays, rectal palpation and serum alkaline and acid phosphatase assessment at 6-monthly intervals. Bone scans were performed every 12 months.

Progression of disease was defined as follows: appearance of biopsy proven local recurrence, appearance of distant metastasis on chest X-rays or bone scans, elevation of previously normal acid phosphatase (later on in combination with elevation of PSA) and alkaline phosphatase.

Disease-free survival life tables and corrected overall survival life tables were calculated according to the method of Kaplan and Meier. The statistical method used was the log-Rank test.

To study the impact of microinvasion of the capsule, category pT3 (according to UICC criteria) was divided into a pT3.1 category (invasion of the capsule) and a pT3.2 category (transgression of the capsule and tumour spread beyond and/or tumour infiltration of the seminal vesicles). All histological specimens were re-examined in serial sections by one of the authors (M.M.).

To study the influence of minimal lymph node metastasis, category pN1 (metastasis in 1 unilateral lymph node) was divided into pN1.1 (micrometastasis in 1 unilateral lymph node with a diameter of 5 mm or less) and a pN1.2 (unilateral in 1 lymph node with a diameter of more than 5 mm eventually visible macroscopically or palpable).

Results

The relation between pathohistological category and the presence of lymph node metastasis is shown in Table 1. In contrast to the clinical staging, most patients (78/117, 68%) had tumour spread beyond the capsule (pT3 disease); 73 (62.3%) had a high, 38 (32.8%) a moderate and 6 (4.9%) a low tumour grade. In only 4 patients with localised carcinoma of the prostate were lymph node metastases detectable. Dividing category pT3 into pT3.1 and pT3.2 revealed that 21/28 patients in the pT2 group had to be reclassified and placed in a higher category (Table 2). Most of the patients in category pT3 were unchanged: 68/78 fell into the new pT3.2 category, 1 patient had to be changed to pT2 and another to pT4.

Table 1 pT Category versus Lymph Node Metastasis

		N neg	*N pos*
pTO	1	1	
pT1	9	8	1
pT2	28	25	3
pT3	78	35	43
pT4	1		1

Table 2 pT (UICC) Versus New pT

		pT2	*pT3.1*	*pT3.2*	*pT4*
pT1	9	2	1	1	
pT2	28	7	19	2	
pT3	78	1	8	68	1
pT4	1			1	

pT3 1 Microinvasion of capsule.
pT3.2 Tumour spread beyond capsule.

With regard to disease-free survival, a maximum follow-up period of 9 years (median 3 years 11 months) (Fig. 1) revealed that all patients in categories pT1 and pT2 exhibited neither local tumour recurrence nor lymph node or bone metastasis.

A different pattern was seen in pT3 patients, where 72% of those in category pT3.1 were free of disease for up to 9 years, in contrast to only 26% in category pT3.2 (median surveillance time for category pT3.1: 4 years, 2 months; pT3.2: 3 years).

A similar situation was found with regard to the corrected overall survival rate (tumour-related death only) (Fig. 2). All patients in categories pT1 and pT2 have survived to date and 86% of those in

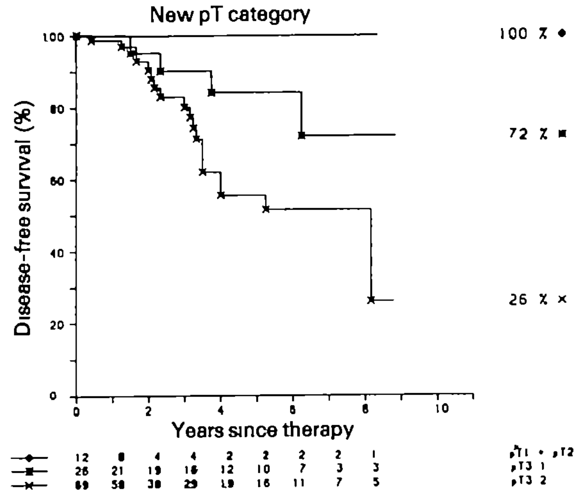

Fig. 1 Disease-free survival in relation to categories pT1, pT2, pT3 1 and pT3 2.

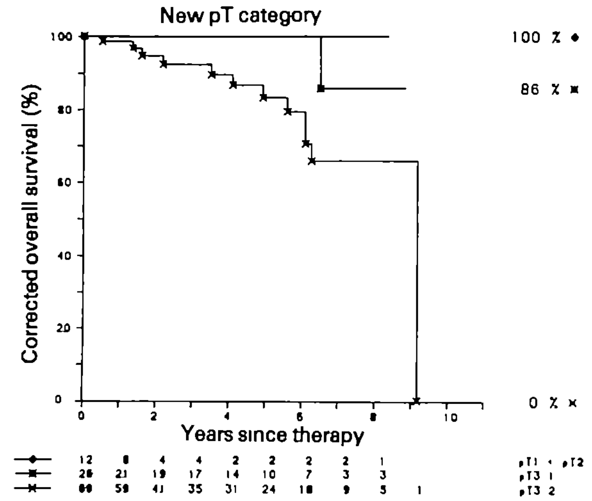

Fig. 2 Corrected overall survival (tumour-related death only) in relation to categories pT1, pT2, pT3 and pT3.2.

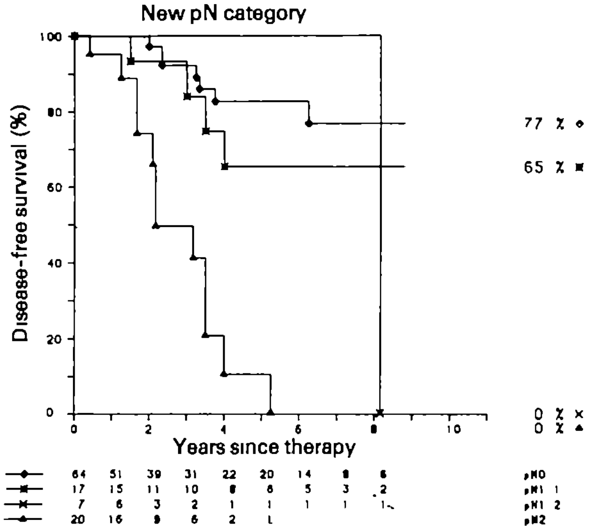

Fig. 3 Disease-free survival in relation to lymph node metastasis (pN0, pN1 1, pN1.2 and pN2)

category pT3.1. In contrast, all patients in category pT3.2 died within 9 years, the first tumour-related death occurring in the first year after radical prostatectomy.

After separating category pN1 into pN1.1 and pN1.2, all resected lymph nodes in categories pT3.1 and pT3.2 were reclassified (Table 3). Most of the pT3.2 patients were placed in categories pN1.2 and pN2.

As far as disease-free survival was concerned, there was no statistically significant difference between categories pN0 and pN1.1. Up to 8 years after radical prostatectomy, 77% of the pN0 patients and 65% of the pN1.1 patients are without local or distant recurrence. Patients in category pN1.2 had a similar prognosis to those in pN1.1; all were recurrence-free during the same observation time (Fig. 3).

By comparison, all patients with bilateral lymph node metastasis at radical prostatectomy showed progress 5 years after radical prostatectomy, the first signs appearing 6 months after surgery.

A similar situation was found regarding the corrected overall survival rate (Fig. 4). Nine years after radical prostatectomy, 81% of the pN0 patients, 80% of the pN1.1 patients and 100% of the pN1.2 patients survived; in contrast, only 36% of patients with bilateral lymph node metastasis at surgery survived (median surveillance time for

Table 3 New pT3 Category versus New pN Category

		pNO	*pN1 1*	*pN1 2*	*pN2*
pT3 1	26	22	3	1	
pT3.2	69	30	14	6	19

pT3 1 Microinvasion of the capsule.
pT3.2 Tumour spread beyond capsule.
pN1 1 Micrometastasis unilaterally.
pN1 1 Macrometastasis unilaterally.

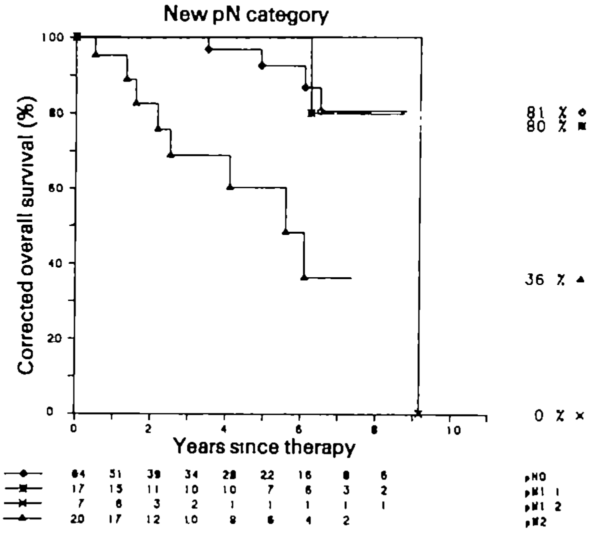

Fig. 4 Corrected overall survival according to lymph node metastasis (pN0, pN1.1, pN1 2 and pN2)

category pN0: 3 years, 4 months; pN1.1: 4 years, 3 months; pN1.2: 1 year, 10 months).

Discussion

The prognosis after radical prostatectomy for patients in categories pT1 or pT2 is favourable. The reported 5-year disease-free survival rate is over 80% (Jewett, 1975; Gibbons *et al.*, 1979; Elder *et al.*, 1982; Middleton and Smith, 1982; Eggleston and Walsh, 1985). The outcome of patients with positive margins or lymph node metastasis is unfavourable (Walsh and Jewett, 1980; Lange *et al.*, 1986). Zincke *et al.* (1984) reported a 5-year survival rate of 60% in patients with positive margins but without tumour infiltration of the seminal vesicles. Comparable, but slightly better results (79% 5-year survival), are reported by Lange *et al.* (1986), who administered adjuvant radiation therapy to patients with positive margins. Only Walsh and Jewett (1980), who considered tumour invasion of the seminal vesicles to be more serious than capsular invasion alone, divided their patients into one group with capsular perforation alone and another with tumour invasion of the seminal vesicles. Their results are comparable to ours: the 9-year survival rate was 86% in patients with microinvasion of the capsule.

Extension of tumour into the capsule of the radical prostatectomy specimen is generally considered to be a matter of concern. However, 5 years after radical prostatectomy all of the patients who showed only invasion of the capsule survived, as did those with a tumour confined to the gland. The outcome was less favourable for patients with tumour spread through and beyond the capsule, where only 83% survived for 5 years.

Nine years after radical prostatectomy, 72% of patients in category pT3.1 are disease-free, in contrast to 26% in category pT3.2.

Lymph node involvement is regarded as a sign of tumour dissemination and has long been considered a situation that precludes radical prostatectomy and pelvic lymyphadenectomy as treatment (Gibbons *et al.*, 1984). Indeed, several studies have shown that radiotherapy given to patients after pelvic lymphadenectomy is of little prognostic benefit (Paulson, 1983; Gibbons *et al.*, 1984; Smith and Middleton, 1985). In contrast, it has been shown that patients with only microscopically detectable regional involvement of the lymph nodes, removed by surgery, achieve long survival times, especially if adjuvant radiotherapy is given (Lange and Narayan, 1983).

Gervasi *et al.* (1985) reported the follow-up of 117 patients with microscopic nodal disease alone after pelvic lymphadenectomy and interstitial Au implanation combined with external radiotherapy. With a mean follow-up of 67 months, the actuarial 5-year disease-free survival rates were 33% for patients with a single microscopically positive lymph node and only 17% for those with multiple microscopically positive nodes.

Our actuarial disease-free survival rates and the corrected overall survival rates of patients with 1 unilateral microscopically positive node are similar to those of patients in category pN0. Nine years after radical prostatectomy and pelvic lymphadenectomy, 65% of the pN1.1 group and 77% of the pN0 group were free of disease.

Eighty-one per cent of patients without nodes and 80% of those with 1 microscopic positive node survived for 9 years after surgery, in contrast to 36% of those with bilateral node disease.

In our experience, microscopic infiltration of the capsule and microscopic disease in 1 unilateral lymph node means no deterioration in the outcome of those patients. Disease-free and overall survival rates in this group are comparable to those of patients with pT2pN0 disease.

If these observations are confirmed by other authors it raises the question of whether the staging systems (which have a prognostic significance, especially the TNM classification) should be re-evaluated.

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The Authors

F. Hering, MD, Assistant Professor of Urology
M. Rist, MD, Assistant Professor of Urology
J Roth, MD, Professor of Radiophysics.
M. Mihatsch, MD, Professor and Chief of Pathology
G Rutishauser, MD, Professor and Chief of Urology.

Requests for reprints to: F. Hering, Department of Urology, Universitätsspital Basel Spitalstrasse 21, CH4031 Basel, Switzerland

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Tumour Markers as Prognostic Aids in Prostatic Carcinoma

A. LEWENHAUPT, P. EKMAN, P. ENEROTH and B. NILSSON

Department of Surgery, Mora Hospital, Mora; Departments of Urology and Cancer Epidemiology, Karolinska Hospital; Unit for Applied Biochemistry, Huddinge Hospital, Stockholm, Sweden

Summary—Of 102 patients suffering from prostatic carcinoma, complete data on the serum concentration of 7 tumour markers were available from 90 patients, together with tumour grade, local stage and the presence or absence of skeletal metastases. The serum content of prostatic acid phosphatase, prostate specific antigen, neopterin, thymidine kinase, osteocalcin, C-reactive protein and tissue polypeptide antigen was measured. By means of Cox's regression and multivariate analysis the ability of these variables to predict prognosis, *i.e.* death from prostatic cancer, was studied.

Neopterin appeared to be the most efficient marker, followed by tumour grade, thymidine kinase and prostate specific antigen. No other variable provided information of statistical significance. In multivariate analysis thymidine kinase performed best, followed by neopterin, tumour grade and prostate specific antigen.

Several serum tumour markers reflect the biological activity of human prostate cancers and their value should be further explored. They may become useful in the management of individual patients.

Since prostate cancer has such a variable and unpredictable course, treatment varies considerably. There is no general agreement on the choice of treatment either in local or widespread disease. It is possible that a marker indicating the biological activity of individual tumours could help to distinguish between tumours with a potential for slow progression and those that progress rapidly, leading to early death. If such markers were identified and introduced into clinical practice, the choice of treatment should be simplified.

In the management of prostatic carcinoma, prostatic acid phosphatase (PAP) has been widely used throughout the last 50 years as a means of following tumour progression or regression (Gutman *et al.*, 1936). Following the development of more sensitive immunological tests, PAP was advocated in the late 1970s as a marker for prostate cancer in health screening surveys (Foti *et al.*, 1977). However, this hypothesis was abandoned because of the high number of false positive and false negatives (Gittes, 1983). Prostate specific antigen (PSA), a new and apparently more specific marker, has recently aroused interest and has been described as superior to PAP both in detecting disease and in signalling relapse (Ferro *et al.*, 1987). Since PSA is elevated in most patients with benign prostatic hyperplasia (Stamey *et al.*, 1987), it is of limited value in detecting disease because the number of false positives is very high. Raising the cut-off levels reduces the number of false positives but leads to an increased number of false negatives. A major advantage of PSA appears to be its unique ability to indicate residual disease following radical prostatectomy for prostatic carcinoma (Stamey *et al.*, 1987).

Several other tumour markers have been found to be more or less valuable in predicting the natural course of prostatic carcinoma. The purpose of this study was to evaluate, by statistical means, the

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prognostic value of various serum markers in prostatic carcinoma. It is unlikely that 1 single marker will be able to distinguish "good" from "bad" tumours, but it is possible that some of them could provide information regarding the biological potential of the tumour for the individual patient (Lewenhaupt *et al.*, 1985b). Apart from PAP and PSA, we have studied neopterin, osteocalcin, thymidine kinase, C-reactive protein (CRP) and the non-specific tumour marker tissue polypeptide antigen (TPA). CA-50 was enrolled in the original series, but was excluded from the final statistical evaluation because of incomplete data and a poor performance.

Neopterin is a protein secreted by activated T-lymphocytes as a sign of an immunological response to tumour associated antigens (Huber *et al.*, 1983). An increase in the serum content of neopterin does not signal an increased ability of the immune system to defeat the tumour but rather an increased outflow of tumour antigens foreign to the species, and thus a more aggressive tumour type (Conrad *et al.*, 1984). Osteocalcin is a Gla-protein indicating increased osteoblastic activity (Deftos *et al.*, 1982). Thymidine kinase and CRP are both elevated when DNA proliferation is increased and thus indicate active tumour regeneration (Gronowitz *et al.*, 1984; Uhlenback and Dati, 1988). TPA and CA-50 are non-specific and not tumour associated markers, probably reflecting increased cell turnover and autolysis (Lüning and Nilsson, 1983; Nilsson *et al.*, 1985).

Tumour grade and local stage are, apart from the patient's age, the most common variables by which the choice of therapy for prostatic carcinoma is made. The performance of various serum tumour markers should, therefore, be compared with these well established prognostic parameters. The aim of this study was to define which serum markers would best distinguish prostate cancers with rapid progression from those with a slow progressive potential. The presence or absence of metastases, as demonstrated by bone scan, was also included in the comparison of prognostic performance.

Patients and Methods

The series comprised 102 patients with prostatic cancer who were followed up for at least 3 years from the time of diagnosis and start of treatment. Before starting treatment, blood samples were drawn and the serum analysed with regard to content of 8 different tumour markers. The patients were participating in a randomised trial comparing the side effects of oestrogen treatment with those of orchiectomy. Patients with concomitant disorders, such as metabolic and cardiovascular disease, or other malignancies, were excluded. Skeletal metastases were found in 31 patients (30%) by means of bone scan and skeletal X-ray. Tumour grade was evaluated by fine needle aspiration biopsy and tumour stage by digital rectal examination only. Excluding CA-50, complete data were available from 90 patients. Follow-up exceeded 3 years in all cases (range 36–73 months).

The markers studied were prostatic acid phosphatase (PAP, Hoechst AG, Frankfurt aM, West Germany) and C-reactive protein (CRP, Sophar, Brussels, Belgium) as analysed by ELISA techniques; prostate specific antigen (PSA, Diagnostic Prod, Inc., Los Angeles, USA), neopterin (Henning AG, Berlin, West Germany), osteocalcin (INC, Stillwater, Minnesota, USA) and thymidine kinase (Sangtec, Bromma, Sweden) were all analysed by radio immunoassays (RIA). The non-specific marker, tissue polypeptide antigen (TPA, Sangtec, Bromma, Sweden), was tested by an RIA technique, since it had performed better than PAP in a previous study (Lewenhaupt *et al.*, 1985a).

The cut-off values for the serum markers used to discriminate between "elevated" and "normal" levels were optimised (PetitClark and Wilding, 1984) to predict 3-year survival as described previously (Ekman *et al.*, 1988; Lewenhaupt *et al.*, 1990). The discrimination limits were calculated from the test's sensitivity versus its specificity (Fig.) (Ekman *et al.*, 1988). The sensitivity of a test is calculated as the number of true positives (in this study patients with elevated markers who died within 3 years) divided by all deceased. The specificity of a test is calculated as the number of true negatives (in this study patients with normal marker levels who survived beyond 3 years) divided by the total number of survivors. The efficiency of the test is calculated from the relative number of deceased in the series. The selected cut-off values were based on a series of patients in which 15 of 82 (17%) were dead from prostate cancer within 3 years. Table 1 shows the results of efficiency testing for various cut-off values for PAP, PSA, osteocalcin, neopterin and TPA (Lewenhaupt *et al.*, 1990). The discrimination limits had to be raised for the following markers: for PAP up to 10 μg/l, PSA 50 μg/l, neopterin 12 nM/l and TPA 120 U/l; the recommended cut-off values could be used for osteocalcin (5 μg/l), thymidine kinase (5 U/l) and CRP (20 mg/l). It should be noted that the Figure presents data on efficiency testing for predicting

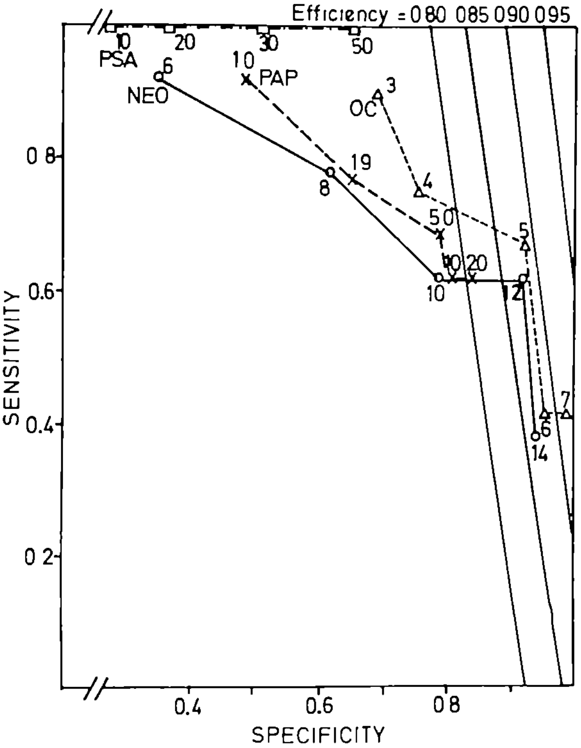

Fig. Calculations of the efficiency of various markers at different cut-off levels to predict short-term prognosis Data calculated on 2-year survival. After 2 years 13% of the patients had died from prostatic carcinoma. PSA = prostate specific antigen, PAP = prostatic acid phosphatase; OC = osteocalcin; NEO = neopterin. (From Ekman *et al.*, 1988).

Table 1 Diagnostic Performance Characteristics which Depend on the Prevalence of Disease at Different Discrimination Limits Based on 3-year Survival (From Lewenhaupt *et al.*, 1990)

Marker	*Discrimination values*	*PV(+)*	*PV(−)*	*Efficiency*
PAP	1.9	26	95	56
(μg/l)	5.0	31	92	67
	10.0	44	92	79
	15.0	46	91	81
	20.0	44	90	80
PSA	10	22	95	41
(μg/l)	25	25	96	52
	50	36	98	71
Osteocalcin	3	31	92	67
(μg/l)	4	39	90	77
	5	58	90	85
	6	54	87	83
	7	87	87	87
Neopterin	8	27	90	62
(nmol/l)	10	33	89	73
	12	58	90	85
	14	50	87	83
TPA	80	31	92	66
(U/l)	100	26	86	70
	120	38	87	78
	140	33	86	77

PV(+) = Specificity, number of patients with normal markers who survived beyond 3 years divided by all survivors.
PV(−) = Sensitivity; number of patients with elevated markers who died within 3 years divided by all deceased.
Efficiency: calculated from a death rate of 17% within 3 years.

survival after 2 years, whereas Table 1 gives the 3-year data. The difference concerning optimal prognostic cut-off values is minimal.

Statistics

Cox's bivariate and multivariate analyses (Cox, 1972) were used to predict survival on data. All continuous variables were dichotomised. The cut-off values were selected as optimised for prediction of survival beyond 3 years (Lewenhaupt *et al.*, 1990).

Results

After 3 years, 18% of the patients (16/90) had died from prostatic cancer. After 4 years, 35% (19/55) were dead and after 5 years 49% (20/41) had died. No deaths from intercurrent disease were recorded during this time.

For all markers tested there was a significant difference in outcome when comparing patients with elevated marker levels with those with normal values ($P < 0.05$). This was true also for tumour grade and the presence or absence of metastases, but not for tumour stage ($P = 0.72$). In simple unadjusted Cox's regression analysis, neopterin had the highest χ^2 value (24.06), followed by metastases (20.12), thymidine kinase (18.85) and osteocalcin (18.06) (Table 2).

In a stepwise Cox's regression analysis, when controlling for neopterin, tumour grade had the highest χ^2-value (14.30), followed by PSA (9.80), metastases (8.61) and thymidine kinase (7.86) (Table 3). No other marker provided information of statistical significance ($P > 0.05$).

When controlling for both neopterin and tumour grade, only thymidine kinase (6.77), metastases (5.74) and PSA (5.17) gave significant information (Table 4).

When thymidine kinase was also in the equation, PSA gave the best performance (5.11) followed by

Table 2 Cox's Bivariate Regression Analyses of Serum Tumour Markers, Tumour Grade and Stage, and Presence or Absence of Metastases as Related to Prediction of Short-term Survival

Variable	χ^2	*P*
Neopterin	24.06	0.0000
Metastases*	20.12	0.0000
Thymidine kinase	18.85	0.0000
Osteocalcin	18.06	0.0000
PSA	15.20	0.0001
Tumour grade*	14.79	0.0001
C-reactive protein	13.70	0.0002
PAP	8.95	0.0028
Tissue polypeptide antigen	4.38	0.0363
Tumour stage*	0.13	0.7211

*Coding Metastases no = 0, yes = 1, Tumour grade (WHO) 1 + 2 = 0, 3 = 1; Tumour stage 1 + 2 = 0, 3 + 4 = 1.

metastases (4.04) (Table 5). After PSA no other marker carried any additional information of statistical significance ($P > 0.05$).

The 4 markers carrying complementary information of statistically significant importance were neopterin, tumour grade, thymidine kinase and PSA. When comparing them by means of multivariate analysis, thymidine kinase performed best ($P = 0.0126$), followed by neopterin ($P = 0.0159$), tumour grade ($P = 0.0256$) and PSA (0.0319) (Table 6). The difference in performance was not statistically significant.

Discussion

The controversy in today's literature on the treatment of localised and generalised prostatic cancer can to a large extent be explained by the unpredictability of the disease and the heterogeneity of the patients. Could patients at high risk for progressive disease be identified, separated from those with a low risk of progression and treated accordingly, the evaluation of various forms of treatment might become more clear-cut and perhaps less controversial. This would have a direct impact on the choice of treatment in the individual case.

Death from prostatic cancer will eventually come for all patients with this disease, provided they survive long enough. Thus, a critical task will be to decide if and when treatment should be commenced. The time limit used in this study was arbitrarily set at 3 years, since this should reflect the difference between patients with rapid and slow tumour progression. Another reason for selecting 3 years was that, in life table analyses, the markers seemed to perform best at 3 to 4 years; thereafter the curves had a tendency to approach each other again (Lewenhaupt *et al.*, 1985a).

Cut-off values for serum markers as suggested by the manufacturers of the commercially available kits are based on healthy normal subjects, since the test is designed for the detection of disease. When evaluating the prognostic performance of a test, the cut-off values have to be based on a comparison within a diseased population (PetitClark and

Table 3 Cox's Regression Analysis of same Variables as in Table 1 when Controlling for the Information from Neopterin in the Calculations

Variable	χ^2	*P*
Tumour grade	14.30	0.0002
PSA	9.80	0.0017
Metastases	8.61	0.0034
Thymidine kinase	7.86	0.0051
PAP	3.75	0.0528
Osteocalcin	2.30	0.1297
C-reactive protein	1.77	0.1834
Tissue polypeptide antigen	0.16	0.6894
Tumour stage	0.03	0.8662

Table 4 Cox's Stepwise Regression Analysis of same Variables as in Table 1 when Controlling for Information from Neopterin and Tumour Grade in the Calculations

Variable	χ^2	*P*
Thymidine kinase	6.77	0.0093
Metastases	5.74	0.0166
PSA	5.17	0.0230
PAP	2.69	0.1008
C-reactive protein	0.91	0.3405
Osteocalcin	0.63	0.4279
Tissue polypeptide antigen	0.17	0.6794
Tumour stage	0.09	0.7660

Table 5 Cox's Stepwise Regression Analysis of same Variables as in Table 1 when Including Neopterin, Tumour Grade and Thymidine Kinase in the Calculations

Variable	χ^2	*P*
PSA	5.11	0.0239
Metastases	4.04	0.0445
PAP	1.53	0.2166
Tissue polypeptide antigen	0.67	0.4148
C-reactive protein	0.51	0.4735
Tumour stage	0.15	0.7000
Osteocalcin	0.05	0.8300

Table 6 Multivariate Analysis of Statistically Significant Parameters in Predicting Short-term Survival

Variable	χ^2	*P*
Thymidine kinase	6.23	0.0126
Neopterin	5.82	0.0159
Tumour grade	4.98	0.0256
PSA	4.60	0.0319

Wilding, 1984). In this study the standard cut-off values were not used; in their place we used the optimal cut-off values calculated from the test's ability to indicate short-term prognosis (rapid progress). This was equal to cancer death within 3 years (Lewenhaupt *et al.*, 1990). As a result of this the discrimination levels have been raised for most markers.

This study has confirmed the impact of tumour grade on prognosis in prostate cancer; patients with poorly differentiated tumours fared much worse than those with well differentiated tumours (Esposti, 1971). However, neopterin, thymidine kinase and PSA seemed equally efficient at reflecting the short-term prognosis. It should be noted that the assay technique for PSA used in this study has in recent years been replaced by more efficient and sensitive monoclonal and polyclonal assays (Chan *et al.*, 1987) and this might have improved performance with regard to prognostic information.

Somewhat surprisingly, tumour stage at the time of diagnosis was poorly related to the clinical course of the individual patient. Tumour volume has been regarded as a major prognostic indicator (McNeal *et al.*, 1989), small tumour volume being virtually harmless whereas large local tumour volume significantly increased the risk of rapid progression. These studies were based on ultrasound examination and meticulous histopathological studies, which are far more accurate than the index finger used for staging in this study. Observations from our own laboratories (Adolfsson *et al.*, 1990) and other publications have questioned the importance of local tumour stage when predicting prognosis (George, 1988). It should be stressed that the statistical evaluation was weighed between low stage tumours (T1–T2) in 1 group versus locally advanced cancers (T3–T4) only; in this situation the index finger should have had a fair chance of making an appropriate staging.

In the first unadjusted comparison of the markers, the presence or absence of metastases was the second most important prognostic parameter. In the final evaluation, metastases did not qualify as a contributing parameter, which might seem surprising. This is explained by the statistical technique used, indicating that the prognostic information covered by the presence or absence of metastases was more efficiently controlled by other markers.

As a result of this study we now analyse neopterin, thymidine kinase and PSA on a routine basis in all patients with newly diagnosed prostatic cancer. Patients enrolled in surveillance protocols have these markers tested on a yearly basis. Once therapy has started, only PSA is analysed with regard to tumour progression or regression, being the only prostate specific tumour marker of the 3. The value of measuring neopterin and thymidine kinase for tumour progression or regression has not been fully investigated, but it is unlikely that these tests will contribute significantly to PSA, which has proved to be a most reliable marker in this respect (Killian *et al.*, 1986).

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The Authors

A. Lewenhaupt, MD, Consultant Urologist and General Surgeon, Mora Hospital.

P. Ekman, MD, PhD, Associate Professor in Urology, Karolinska Hospital

P. Eneroth, PhD, Professor in Biochemistry, Karolinska Institute.

B Nilsson, PhD, Statistician, Department of Cancer Epidemiology, Karolinska Institute

Requests for reprints to: A. Lewenhaupt, Department of Surgery, Mora Hospital, S-792 00 Mora, Sweden

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Serum Acid Phosphatase in Patients with Localised Prostatic Cancer, Benign Prostatic Hyperplasia or Normal Prostates

J. O. SALO, S. RANNIKKO and R. HAAPIAINEN

Second Department of Surgery, Urological Unit, Helsinki University Central Hospital, Helsinki, Finland

Summary—Serum acid phosphatase levels were determined in 247 men with surgically confirmed intracapsular prostatic cancer (30 patients), benign prostatic hyperplasia (BPH) (114 patients) or palpably normal prostates (103 men). Both radioimmunoassay (245 cases) and an enzymatic method (218 cases) were used. Using radioimmunoassay, the mean serum prostatic acid phosphatase (PAP) level was significantly higher in patients with BPH than in patients with intracapsular cancer or men with normal prostates. The weight of hyperplastic tissue removed during operation in the BPH group correlated closely with PAP concentrations. Age or the presence (or absence) of an indwelling catheter had no effect on PAP concentrations. Using the enzymatic method, the highest levels of acid phosphatase were also detected in patients with BPH but the difference was less marked.

It was concluded that intracapsular cancer does not elevate serum acid phosphatase levels as determined by radioimmunoassay or an enzymatic method. BPH alone leads to significant rises in PAP concentrations. The degree of BPH correlates with PAP levels.

Acid phosphatases are exocrine products of the normal prostate. They form a group of non-specific enzymes that hydrolyse phosphate esters under acid conditions to yield inorganic phosphate. Their physiological function has not been clarified but they have been found useful for staging and monitoring prostatic cancer. They were the first tumour marker to be studied in urology (Gutman *et al.*, 1936; Huggins and Hodges, 1941). Both enzymatic and radioimmunoassay techniques have been used to measure acid phosphatases. There is disagreement over whether or not immunochemical techniques are any better than enzymatic methods (Quinones *et al.*, 1981; Samuell *et al.*, 1984; Vihko *et al.*, 1985). Until recently it has not been clear whether serum acid phosphatase levels in localised prostatic cancer differ from those in benign prostatic hyperplasia and in subjects with normal prostates (Bruce *et al.*, 1981).

In this study we compared serum levels of acid phosphatase, measured by both enzymatic and radioimmunoassay techniques, in patients with histologically verified BPH, in patients with surgically staged intraprostatic cancer and in men with clinically normal prostatic glands.

Patients and Methods

Acid phosphatase levels were determined in 247 patients whose mean age was 62.5 years (range 18–88). Thirty patients (mean age 66 years, range 53–75) had intracapsular prostatic cancer, confirmed by histological examination of radical prostatectomy and pelvic lymphadenectomy specimens. The tumours were well differentiated (Grade 1) in 12 cases, moderately differentiated (Grade 2) in 16 and poorly differentiated (Grade 3) in 2 cases; 114 patients (mean age 70 years, range 54–86) had BPH, verified by histological examination of material obtained either through transurethral resection of

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the prostate (110 cases) or by transvesical prostatectomy (4 cases). Thirty-seven of these BPH patients (32%) had had a pre-operative indwelling catheter because of urinary retention. Weights of tissue obtained during operation were recorded. Acid phosphatase levels were also determined in 103 patients (mean age 54 years, range 18–88) with various non-prostatic diseases and palpably normal prostates (controls). An enzymatic method was used in 218 cases and radioimmunoassay (RIA, Farmos, Oulunsalo, Finland) in 245 cases to measure acid phosphatase levels.

The χ^2 test, analysis of variance and regression analysis were used for statistical analysis of the results. Natural logarithmic transformations were used in calculations to reduce skewness when appropriate.

Results

Radioimmunoassay

The PAP values in the various diagnostic groups are shown in Figure 1. Mean PAP levels in the intracapsular prostatic cancer, BPH and control groups were 1.8, 2.3 and 1.7 µg/l respectively (Table 1). The mean PAP level in the BPH group was significantly higher than the levels in the other groups ($P<0.0001$).

Regression analysis showed age to have no effect on PAP levels in any group. In patients with BPH, prostatic size correlated with PAP levels ($r=0.415$, $P<0.001$) but the presence (or absence) of an indwelling catheter had no effect on PAP levels (Fig. 2).

In the control group the mean PAP level was, as stated above, 1.7 µg/l. The standard deviation (SD) was 0.5 µg/l. Defining an upper limit for normal values as the mean +2 SD, values above 2.7 µg/l were regarded as elevated. Elevated PAP values were encountered in 8/30 patients (27%) with localised cancer, in 27/114 patients (24%) with BPH and in 5/101 patients (5%) with normal prostates (Table 2).

Enzymatic method

The mean levels of acid phosphatase as measured by the enzymatic method were 7.8, 8.5 and 7.7 iu/l in the localised cancer, BPH and control groups respectively. In the BPH group the mean acid phosphatase level was significantly higher than in the other diagnostic groups ($P=0.04$).

Regression analysis showed that neither age,

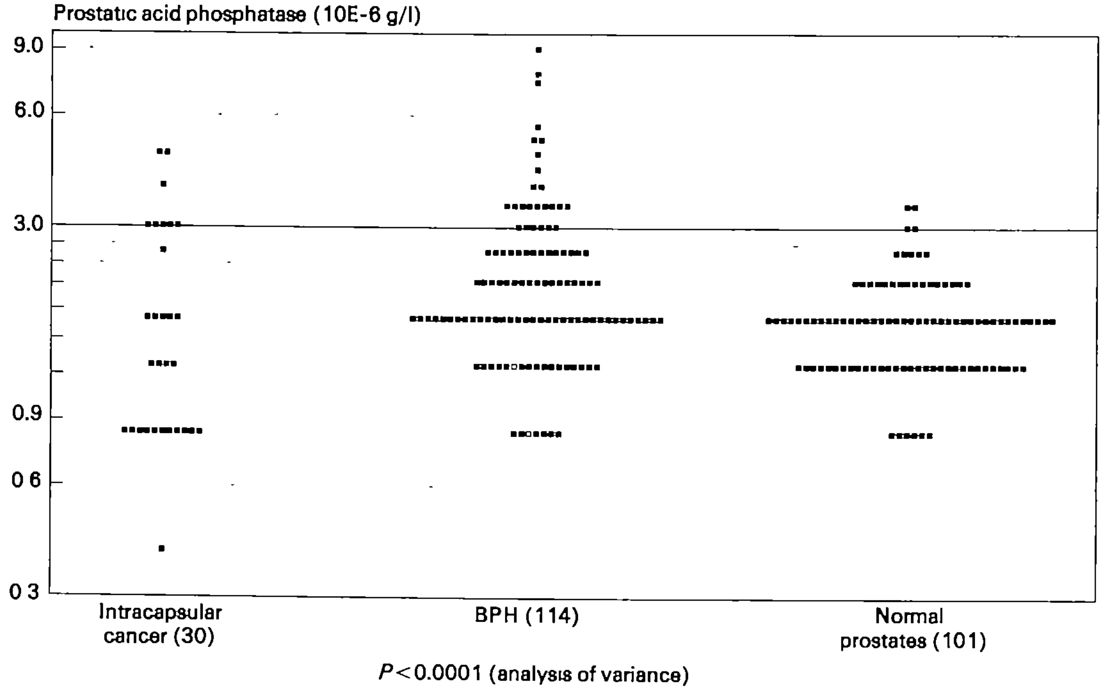

Fig. 1 Histograms of serum prostatic acid phosphatase concentrations in men with intracapsular cancer, benign prostatic hyperplasia or palpably normal prostates

Table 1 Acid Phosphatase Levels in Various Diagnostic Groups

	RIA (μg/l)				*Enzymatic method (iu/l)*			
	Mean	*Range*	*SD*	*No*	*Mean*	*Range*	*SD*	*No.*
Intracapsular cancer	1.8	0.4–4.7	1.2	30	7 8	6.0–11.0	1 4	19
BPH	2.3	0.7–9.1	1.3	114	8.5	4.0–15.0	2.4	100
Controls (normal prostates)	1.7	0.8–3 4	0.5	101	7.7	4.0–14 0	1.9	99

weight of hyperplastic tissue removed during operation, nor the presence (or absence) of an indwelling catheter had any effect on acid phosphatase levels measured enzymatically in BPH patients.

In the control group the mean acid phosphatase level was, as stated above, 7.7 iu/l. The SD was 1.9 iu/l. Values over 11.6 iu/l (mean + 2 SD) were therefore considered abnormal. No abnormally elevated values were seen in any patient with localised cancer (measurements made in 19 patients). In 100 BPH patients the acid phosphatase level was elevated in 12 cases (12%). In 99 patients with normal prostates it was elevated in 2 cases (2%).

Discussion

The value of determining acid phosphatase levels in the detection of metastatic prostatic carcinoma and in the follow-up of prostatic cancer patients has been well documented (Vihko *et al.*, 1985; Siddall *et al.*, 1986). Radioimmunoassay techniques have usually been found to be more sensitive than enzymatic methods in detecting metastatic disease (Killian *et al.*, 1982; Moon *et al.*, 1983; Vihko *et al.*, 1985).

Elevated PAP levels have also been found to predict, with a high degree of probability, local extension outside the prostate or lymph node metastases in patients in whom findings were negative after bone scintigraphy and pelvic computed tomographic scanning (Salo and Rannikko, 1988).

In the present study it was found that the highest acid phosphatase levels occurred in patients with BPH. These findings are in accordance with those of Reif *et al.* (1973), who measured acid phosphatase activity in hyperplastic tissue, primary prostatic cancer tissue and normal prostate tissue and established that hyperplastic tissue had the highest acid phosphatase activity, followed by normal prostate tissue, with cancer tissue having the lowest

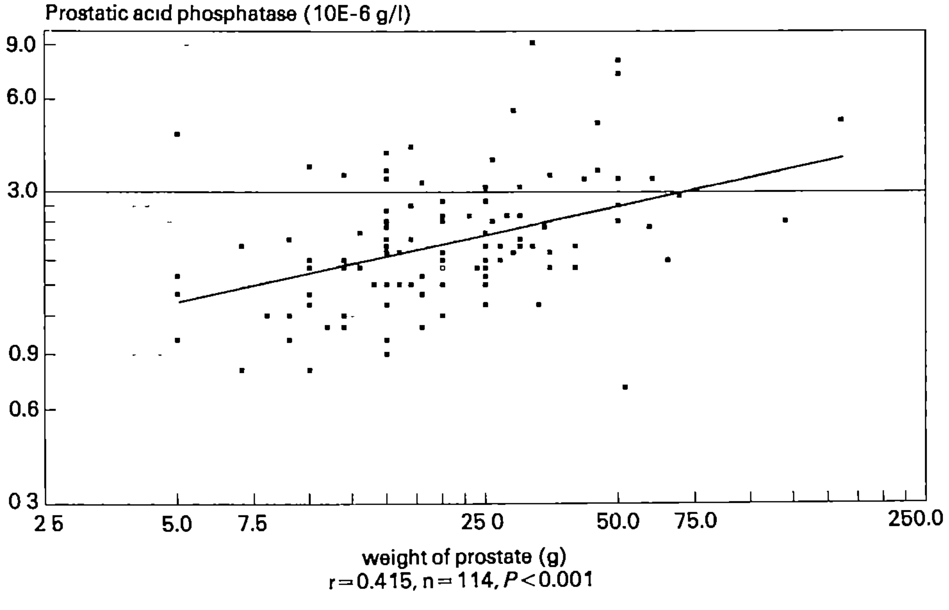

Fig. 2 Correlation between serum prostatic acid phosphatase concentrations and weight of hyperplastic prostates on operation

Table 2 Patients with Elevated Acid Phosphatase Levels in Different Diagnostic Groups

	Intracapsular cancer (%)	*BPH (%)*	*Controls (normal prostates) (%)*
RIA (>2.7 µg/l)	8/30 (27)	27/114 (24)	5/101 (5)
Enzymatic method (>11.6 iu/l)	0/19 (0)	12/100 (12)	2/99 (2)

activity. It has been found using enzymatic (Downey *et al.*, 1954) and immunochemical assays (Reif *et al.*, 1973; Foti *et al.*, 1977) that acid phosphatase levels are 7 to 20% lower in prostatic cancer than in hyperplastic tissue. In the present series the mean levels of serum PAP were higher in BPH than in prostatic cancer patients, but there was no difference in percentages of elevated values in these 2 groups.

Several explanations have been suggested for the apparently paradoxical finding that serum acid phosphatase levels are elevated in advanced prostatic cancer (increased mass of prostatic tissue, ductal obstruction, extension into periprostatic fat, the lymphatics and blood vessels). The most important factors may be those leading to increased release of the enzyme into the circulation (Heller, 1987). It has been found in ultrastructural studies that malignant acini lose the polarity of their secretion and tend to secrete acid phosphatase towards the basement membrane rather than towards the acinar lumen. In addition, cancer cells which have invaded the prostatic stroma or infiltrated outside the prostate have lost their connection with the ductal system. Acid phosphatases are therefore secreted directly into the interstitium and thence into the blood stream. In early stage intracapsular cancers, no rise in serum acid phosphatase levels is seen, but the greater the tumour mass, the higher the serum acid phosphatase concentration (Samuell *et al.*, 1984; Salo and Rannikko, 1988).

In early studies using radioimmunoassay (Vihko, 1978), counterimmunoelectrophoresis (Killian *et al.*, 1980) and solid-phase immunofluorescent assays (Lee *et al.*, 1980), high percentages of elevated concentrations of PAP were found in cases presumed to be of localised cancer. In the present study, elevated PAP values were detected in 27% of patients with localised cancer confirmed by histological examination of operative specimens. In many earlier studies, staging was based only on the results of bone scanning and rectal examination. Pelvic lymphadenectomy and radical prostatectomy were not performed. It is possible that many patients presumed in these studies to have localised cancer and who exhibited elevated PAP concentrations in fact had unrecognised extracapsular extension of the disease.

The promising results of the early radioimmunoassay studies are in conflict with those of later studies (Heller, 1987). In prostatic cancer patients, it would seem that in most cases increased amounts of acid phosphatase are not secreted into the blood stream until the primary tumour has invaded outside the gland or metastasised. Acid phosphatase determination therefore has no role as a screening method for detection of early intracapsular prostatic cancer.

The finding in this study that acid phosphatase levels were higher in BPH patients than in younger men with normal prostates may reflect a bigger mass of glandular tissue in the hyperplastic glands. This would be in accordance with the finding that the size of the hyperplastic prostates correlated positively with PAP levels. It has even been suggested that reference should be made to PAP concentrations in men with BPH rather than to those in men with normal prostates when defining the upper limit of normal PAP concentration (Heller, 1987). If the upper limits in our series had been defined using acid phosphatase levels in patients with BPH, they would have been 4.9 µg/l and 13.3 iu/l using the radioimmunoassay and enzymatic methods respectively. On this basis, only PAP values over 4.9 µg/l in men with clinically evident BPH would be regarded as elevated. Only above that level would elevated PAP levels be more likely to reflect advanced prostatic cancer than BPH. According to these criteria, none of our patients with intracapsular prostatic cancer had elevated PAP levels.

There has been some disagreement about the effect of urinary retention and insertion of an indwelling catheter on acid phosphatase levels. Greatly elevated serum acid phosphatase levels have been found in cases of prostatic infarction with urinary retention (Vihko and Kontturi, 1981; Collier and Pain, 1986). The present study revealed no difference in acid phosphatase levels in patients with or without an indwelling catheter. Use of a catheter, therefore, does not in itself lead to any rise in acid phosphatase levels. This is in accordance with the finding that PAP levels return to previous values within 1 to 2 days of relieving urinary retention by means of an indwelling catheter (Heller, 1987).

It is concluded that BPH leads to significant rises in serum PAP levels compared with those seen in cases of localised prostatic cancer or in controls with normal prostates. The degree of hyperplasia correlates positively with PAP levels. Elevated acid phosphatase levels are less evident when an enzymatic method is used for determination. Slightly elevated PAP concentrations in patients with clinically evident BPH are probably linked to the hyperplasia. Prostatic cancer need not be suspected.

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The Authors

J. O Salo, MD, Consulting Urologist
S. Rannikko, MD, Consulting Urologist.
R. Haapiainen, MD, Consultant Surgeon, Assistant Lecturer.

Request for reprints to. J. O Salo, Urological Unit, Second Department of Surgery, University Central Hospital, Haartmaninkatu 4, SF-00290 Helsinki, Finland.

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Carcinoma of the Prostate Masquerading as Rectal Carcinoma

Report of 3 Cases and Review of the Literature

M. C. FOSTER and P. H. O'REILLY

Department of Urology, Stepping Hill Hospital, Stockport

Summary—We present 3 patients with prostatic tumours who presented with symptoms of rectal stenosis. In all 3 cases digital examination of the rectum revealed a mass suggestive of rectal carcinoma, but carcinoma of the prostate was suspected because of other clinical features and this was confirmed by biopsy. Treatment by hormonal manipulation resulted in a dramatic improvement in symptoms. The diagnostic and management difficulties associated with this unusual presentation of carcinoma of the prostate are described, together with a review of the literature.

In the majority of cases, carcinoma of the prostate presents with symptoms of bladder outflow obstruction; on rectal examination the prostate gland is usually irregularly enlarged. Primary rectal tumours, on the other hand, often form stenotic lesions which are palpable the whole way around the lumen of the bowel and may obstruct the rectal lumen. We present 3 cases in which prostatic carcinomas presented as stenotic obstructing rectal tumours. Review of the literature confirmed our conclusion that accurate identification of prostatic carcinoma presenting as rectal stricture is vital for appropriate management.

Case Reports

Case 1. A 60-year-old man was referred to a general surgeon with a history of increasing constipation and rectal bleeding. On rectal examination there was a large stenosing tumour mass suggestive of rectal carcinoma but without obvious mucosal involvement. Urological opinion was sought and needle biopsy of the mass revealed prostatic carcinoma (Gleason grade 2–3). Plasma acid and alkaline phosphatase levels were grossly elevated and isotope bone scanning showed multiple skeletal metastases. In the absence of urinary symptoms, subcapsular orchiectomy only was performed. Within 2 weeks the rectal symptoms disappeared. By 3 months acid and alkaline phosphatase had returned to normal and the bone scan reverted to complete normality The patient remains alive and well 18 months later, with normal biochemical tests and a persisting normal bone scan.

Case 2. A 70-year-old man presented to a general surgeon with an inguinal hernia and mentioned that he had a diminished urinary stream and hesitancy. Rectal examination by a urologist suggested that the prostate might be malignant. The hernia was repaired and both transrectal needle biopsy of the prostate and transurethral prostatic resection were performed. Histology of both specimens was benign and the patient made an uneventful recovery. The patient re-presented 31 months later to the same general surgeon with a history of increasing constipation and abdominal distension. Rectal examination revealed a tight stricture consistent with a stenosing rectal carcinoma. There were no urinary symptoms but because of the clinical suspicion of a prostatic malignancy 31 months previously, urological opinion was again sought. On this occasion serum acid phosphatase was elevated and transrectal biopsy showed poorly differentiated carcinoma of the prostate (Gleason grade 4/4) A trial of oestrogen therapy was initiated (tetrasodium fosfestrol 1 g daily intravenously for 5 days, then 100 mg orally 3 times daily). Within 5 days there was a significant improvement in bowel symptoms, with a return to complete normality after 2 weeks. Subcapsular orchiectomy was performed and the oestrogens were stopped. After 20 months, during which time the patient had enjoyed good health with normal clinical, biochemical and scintigraphic assessment, he re-presented with haematuria. Rectal examination suggested local recurrence, confirmed at cystourethroscopy and biopsy. Local external beam radiotherapy was performed with good

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initial response and 6 months later the patient was symptom-free with normal biochemistry, rectal examination, bone scan and NMR scan.

Case 3. A 57-year-old man presented to a general surgeon with increasing constipation, weight loss and general malaise. He had no urinary symptoms. On rectal examination he had a tight rectal stricture which would not admit the examining finger. However, the rectal mucosa seemed mobile. A urological opinion was sought. Prostatic carcinoma was suspected. Bone scanning and acid and alkaline phosphatase were normal. Computed tomography showed abnormal thickening of the perirectal tissues, especially anteriorly where there was involvement of the seminal vesicles. The rectal lumen was compressed to a tiny smooth featureless tube (Fig. 1). Cystourethroscopy was normal. Transrectal prostatic biopsy and transurethral prostatic resection were performed. The chippings from the transurethral resection were benign but the transrectal biopsy showed poorly differentiated adenocarcinoma, not typical of bowel origin but compatible with, though not diagnostic of, prostatic carcinoma. A subcapsular orchiectomy was performed. Within 5 days the patient had resumed spontaneous bowel movements, with a return to normal bowel habit by 2 weeks. Post-operative CT scanning 6 weeks after orchiectomy showed complete resolution of tumour and a return to normal appearances of rectal lumen, rectal wall and seminal vesicles (Fig. 2). The patient remains tumour-free 12 months later.

Discussion

Most prostatic tumours originate in the periphery of the gland (McNeal, 1969; Byar and Mostofi, 1972) and rectal examination is the most important initial step in the clinical diagnosis of prostatic carcinoma. Typically, a hard indurated area is palpable. Stenotic lesions causing rectal obstruction are usually rectal carcinomas (Goligher, 1984). Posterior spread of prostatic carcinoma into the rectum is usually prevented initially by the prostatic capsule and subsequently by Denonvillier's fascia. Thus the tumour tends to spread centrally to involve the gland itself and only then seeks to penetrate the capsule, following which it can spread caudally along the perivesicular sheath and bladder base to obstruct the ureters (Catalona and Scott, 1986; Kozlowski and Grayhack, 1987). Spread towards and into the rectum and circumferential spread around the rectal wall, causing symptoms of rectal obstruction as described in the 3 cases presented here, can also occur. Winter (1957) reported 32 cases of carcinoma of the prostate with rectal involvement "to the extent of creating a problem in differential diagnosis". In 8 cases the prostatic mass protruded directly into the rectal lumen to such an extent that a proctoscope could not be passed beyond the tumour; in 13 cases there was an annular stenosing lesion and in 7 cases the rectal mucosa was involved. In 3 cases prostatic primaries metastasised to the rectum and 1 patient presented with a synchronous prostate and rectal tumour. These patients were part of a series of 225 prostatic tumours; the incidence of true rectal involvement was 10%. Fry *et al.* (1979) reported 13 patients with rectal obstruction secondary to histologically

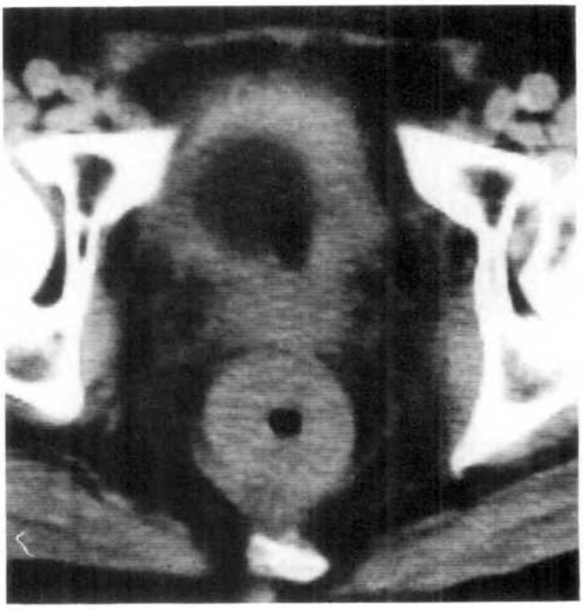

Fig. 1 Computed tomogram of pelvis in case 3 at time of presentation, showing compression of rectal lumen by tumour.

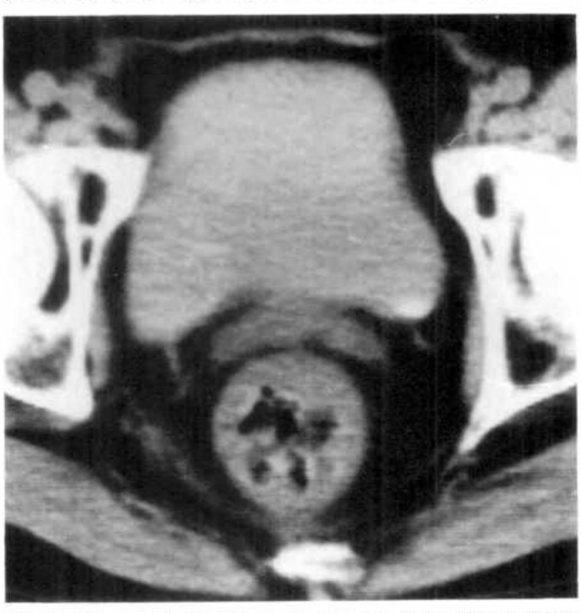

Fig. 2 Computed tomogram in case 3 6 weeks after orchiectomy.

proven prostatic carcinoma. In 10 cases the lesion was annular. In 6 cases the rectal mucosa was ulcerated and in the remainder it was normal. All patients gave a history of abdominal pain and constipation, indicating a significant degree of rectal obstruction. In addition, 6 had rectal bleeding and 6 had no urinary symptoms. Lasser (1978) reported 5 cases of carcinoma of the prostate with rectal involvement, although in 2 cases rectal involvement was associated with tumour recurrence following transurethral resection rather than being present at the time of tumour diagnosis. The incidence of rectal involvement at presentation was 2% (3 cases from a series of 161 prostatic tumours). Further cases have been reported by Mir *et al.* (1973), Sweitzer *et al.* (1977), Reeves and Wheatley (1978) and Siegel *et al.* (1986).

All 3 patients presented here responded to hormonal manipulation either with oestrogens or by orchiectomy, as is true of many of the cases described in the literature. Because of the difficulties which may be encountered in making the correct diagnosis of prostatic carcinoma, inappropriate anterior resection or abdominoperineal resection has been performed in some cases (Mir *et al.*, 1973; Fry *et al.*, 1979). Suspicion that a tumour may be of prostatic origin should be high if the rectal mucosa remains mobile, suggesting that it is not involved, as in our patients. This is not completely reliable, however, and there are reports of primary prostatic tumours ulcerating through the rectal mucosa (Winter, 1957; Lasser, 1978; Reeves and Wheatley, 1978; Fry *et al.*, 1979). Fry *et al.* (1979) and Siegel *et al.* (1986) advised that an intravenous urogram would frequently show ureteric obstruction in cases of prostatic malignancy with rectal involvement, whereas such obstruction was less common in cases of primary rectal carcinoma. Elevation of acid and alkaline phosphatase and of prostatic specific antigen are also indicators of a primary prostatic tumour. As in case 2, biopsies of the rectal lesion may sometimes be unhelpful in determining the site of origin of the tumour (Mir *et al.*, 1973; Sweitzer *et al.*, 1977; Reeves and Wheatley, 1978). Fry *et al.* (1979) recommended that in order to confirm the diagnosis of prostatic carcinoma, tissue as far away as possible from the obstructing rectal lesion should be examined histologically (*i.e.* transperineal or transurethral biopsy); our experience with case 3 suggests that this is not always helpful. Siegel *et al.* (1986), having identified prostatic tumour in a biopsy of a rectal tumour, were able to demonstrate tumour in only 1 of 225 prostatic chips examined after transurethral resection. In 2 of our patients transurethral resection chippings were benign; in 1 case transrectal biopsy was initially benign but became malignant later and in the other, transrectal biopsy was malignant from the outset.

In conclusion, carcinoma of the prostate may occasionally present as a stenotic rectal lesion producing intestinal obstruction, hence masquerading as a primary rectal carcinoma. The patient runs the risk of an inappropriate abdominoperineal resection of the rectum if the true nature of the lesion is not confirmed with its attendant mortality and morbidity—an unnecessary consequence of misdiagnosis. If prostatic carcinoma is correctly diagnosed, the response to treatment by hormonal manipulation is good. Urologists and general surgeons should be alert to this mode of presentation of prostatic tumours.

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The Authors

M. C. Foster, DM, FRCS, Urological Registrar.

P H O'Reilly, MD, FRCS, Consultant Urological Surgeon.

Requests for reprints to. P. H. O'Reilly, Department of Urology, Stepping Hill Hospital, Stockport SK2 7JE.

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Treatment of Stage D2 Prostatic Cancer Refractory to or Relapsed following Castration plus Oestrogens

Comparison of Aminoglutethimide plus Hydrocortisone with Mexdroxyprogesterone Acetate plus Hydrocortisone

W. R. BEZWODA

Department of Medicine, Haematology/Oncology, University of the Witwatersrand Medical School and Johannesburg Hospital, Johannesburg, South Africa

Summary—A total of 59 patients with advanced prostate cancer relapsed from or refractory to castration plus oestrogen were treated in a randomised trial comparing 1000 to 1250 mg aminoglutethimide + 40 mg hydrocortisone (AG + HC) with 500 mg medroxyprogesterone acetate + 40 mg hydrocortisone (MPA + HC). A significantly higher objective response rate and better symptomatic control was noted in patients treated with AG + HC (31%) compared with those treated with MPA + HC (3%). The median time to treatment failure was also significantly longer for patients treated with AG + HC. These findings suggest a role for AG in the treatment of advanced prostate cancer. While both second-line hormone treatment regimens resulted in significant suppression of adrenal androgen secretion, the differences in response rate could not be explained by alterations in peripheral blood hormone levels. AG in high doses may have cellular effects which require further study.

The treatment of symptomatic Stage D prostate cancer which progressed after first-line hormone manipulation remains a problem (Johnson *et al.*, 1977; Klein, 1979; Paulson *et al.*, 1979). A previous randomised study from this institution demonstrated that second-line hormone manipulation using progestogen therapy (medroxyprogesterone acetate) was as effective as chemotherapy consisting of cyclophosphamide + doxorubicin + 5 fluorouracil) (Ruff *et al.*, 1989). The response to second-line treatment regimens including MPA was, however, mostly stabilisation of disease and little influence on survival time was seen. Since MPA had the lowest frequency of subjective side effects and complications, it nevertheless appeared justified to use this therapy as 1 arm of a new study comparing MPA with aminoglutethimide in the treatment of advanced prostate cancer.

Patients and Methods

In a randomised controlled investigation, medroxyprogesterone acetate plus hydrocortisone was compared with aminoglutethimide plus hydrocortisone in patients with symptomatic Stage D2 prostate cancer who had progressed after primary hormone manipulation. The series included 60 patients with biopsy proven, disseminated prostate cancer attending the Oncology Clinic of the Johannesburg Hospital between January 1986 and January 1988. All had either failed to respond to prior orchiectomy and stilboestrol (2 mg/day) or had progressed after prior response. To be eligible for the study, performance status had to be ⩾50 (Karnofsky) plus unequivocal evidence of increase in size of measurable lesions or new lesions on bone scan. Randomisation was by means of the closed envelope random number technique and patients received treatment with either medroxyprogesterone acetate 500 mg/day plus hydrocortisone 40 mg/

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day or aminoglutethimide 1250 mg/day plus hydrocortisone 40 mg/day. Those on the aminoglutethimide arm of the study started at an initial dose of 500 mg AG plus 40 mg HC/day. The AG was increased by 250-mg increments every 2 weeks until a total dose of 1250 mg/day was reached. AG was given in 4 divided doses with the nocturnal dose consisting of 500 mg. Both MPA and HC were given as single doses. The AG dose was increased only if there were no symptoms or side effects at each of the previous dose levels. Patients who had minor symptoms were left on the lower dose until tolerance had developed before attempting the next dose level. Pre-treatment prognostic variables were equally distributed between the 2 groups. The nature of and response to initial treatment was similarly comparable; 27 patients had been treated sequentially by means of orchiectomy followed (after progression) by stilboestrol (2 mg/day) and 33 patients had received stilboestrol starting concurrently with orchiectomy. The median time from initial therapy to admission to the present study and median duration of response to first-line treatment were similar for both study arms (Table 1).

Initial assessment included history and clinical examination, radioisotope bone scan, skeletal X-rays, chest X-ray, abdominal sonography and CT scan (where clinically indicated); biochemical values included acid phosphatase (ACP), alkaline phosphatase (ALP) and prostate specific acid phosphatase (PAP). Screening tests for liver and renal function (automated SMAC) were also carried out. Pain was assessed by means of a visual analogue scale from 0 = no pain to 100 = intractable pain (despite optimal analgesic use) and by recording average daily analgesic usage. Performance status was recorded according to Eastern Co-operative Oncology Group criteria. Clinical examinations, pain scores and biochemical indices were repeated monthly and all radiological and radioisotope examinations were repeated 3-monthly. Response criteria were those proposed by the National Prostate Cancer Project (NPCP) Group (Schmidt *et al.*, 1976). Objective evidence of response included a 50% decrease in the number of lesions on bone scan and/or >50% reduction in measurable soft tissue disease (if both bone and soft tissue disease were present, both criteria had to be met), as well as normalisation of total and/or prostate specific acid phosphatase, together with improvement of pain plus reduction in analgesic usage and disappearance of evidence of non-measurable extraskeletal disease. Stable disease included subjective benefit as defined by a decrease in analgesic usage and improvement or stabilisation of performance status, together with no deterioration of objective measurement of disease status (scan, soft tissue measurements and no increase in tumour markers) for at least 3 months. Statistical methods included χ^2 analysis, analysis of variance and survival analysis using the log rank test of Peto and Pike (Peto *et al.*, 1977).

Table 1 Aminoglutethimide + Hydrocortisone (AG + HC) Versus Medroxyprogesterone Acetate + Hydrocortisone (MPA + HC) for Second-line Therapy in Advanced Prostrate Cancer

	AG+HC		*MPA+HC*	
No of patients	29		30	
Mean age (years)	68.3±2.7		67 7±3.6	
Performance status (Karnofsky)	No.	(%)	No.	(%)
50–59	9	(30)	11	(36.7)
60–69	16	(56.7)	17	(56.7)
70–79	4	(13.3)	2	(6.7)
Metastatic sites				
Bone	24	(83)	25	(83)
Bone and soft tissue	5	(17)	5	(16.7)
ACP elevated	26	(89.6)	27	(90)
PAP elevated	20	(68 9)	21	(70)
ALP elevated	29	(100)	30	(100)
ACP (iμ/ℓ)	16.7±3.7		14.1±3.9	
PAP (iμ/ℓ)	9.2±3.7		9.9±2.2	
ALP (iμ/ℓ)	447 ±143		424 ±97	
Median pain (score)	60		60	
Median morphine usage (mg/24 h)	60		60	
Prior treatment				
Orchiectomy + stilboestrol	18	(60)	15	(50)
Response	12	(66 7)	11	(73.3)
Median duration of response (months)	11		10	
Orchiectomy followed by stilboestrol	12	(40)	15	(50)
Response	6	(50)	7	(46.7)
Median duration of response (months)	7		8	

ACP = Acid phosphatase
PAP = Prostate specific acid phosphatase.
ALP = Alkaline phosphatase

All patients entering the study gave informed consent and the study was approved by the Committee for Ethics of Human Research of the University of the Witwatersrand.

Results

Of the 60 patients in the study, 52/59 were evaluable. One patient randomised to AG + HC was withdrawn because of the development of spinal cord compression prior to starting therapy. A further 3 patients receiving AG were withdrawn after 2 weeks of therapy. One patient on the MPA arm was also withdrawn for early toxicity. Three patients receiving MPA were lost to follow-up and were not evaluable when last seen. Six patients received 1000 mg/day of AG and 2 could only tolerate 750 mg/day before developing unacceptable side effects (mainly drowsiness, dizziness and disorientation). These patients were, however, all included in the evaluation.

Table 2 shows the results of treatment. The overall objective response (PR) was 9/29 (31%) for patients treated with AG+HC compared with 1/30 (3%) for those receiving MPA ($\chi^2=7.92$, $P<0.01$). The 9 patients with >50% improvement in lesions on bone scan showed improvement only after at least 6 months of therapy, but despite objective evidence (as defined) of improvement on bone scan, none returned completely to normal. Changes in total acid phosphatase values on treatment are shown in the Figure. All of the objective responses occurred in patients who had had a prior response to castration and/or oestrogens. In addition to the partial responders, 5/29 (17%) had disease stabilisation on AG+HC while 7/30 (26%) had stable disease on MPA+HC. Only 2 patients who had shown no prior response to first-line treatment achieved disease stabilisation with AG+HC.

When subjective parameters, including pain score and opioid analgesic usage as well as performance status, were compared for the 2 groups, patients treated with AG+HC fared significantly better in all categories. The median time to treatment failure was 9 months for patients receiving AG+HC and 4 months for those receiving MPA+HC ($P<0.05$). There was a strong trend ($P=0.06$) towards longer survival among patients treated with AG+HC.

Table 3 shows plasma testosterone, Δ^4 androstenedione (Δ^4) and dehydroepiandrostenedione-sulphate (DHEAS) levels prior to and 3 months after therapy. AG+HC caused significant suppression of adrenal adrogen secretion in all evaluable patients. Adrenal androgen values after MPA+HC were also suppressed significantly. There were no significant differences in hormone levels between the 2 groups and no significant differences when hormone levels of responders were compared with those of non-responders.

FSH and LH values were significantly suppressed in 14/26 patients receiving AG+HC (including all responders) and 18/22 patients receiving MPA+HC ($\chi^2=5.22$, $P<0.05$).

Side effects of treatment are shown in Table 4. Both second-line hormonal therapies were well tolerated by the majority of patients. Reasons for withdrawal from treatment included recurrent rash and fever (3 patients receiving AG+HC) and fluid retention and oedema (1 patient receiving MPA+HC). No significant haematological or biochemical toxicity was encountered.

Discussion

The present study indicates a role for aminoglutethimide as second-line treatment for patients who progressed after initial hormone manipulation. A higher response rate and a strong trend towards increased survival were demonstrated in patients

Table 2 AG+HC Versus MPA+HC in Prostate Cancer: Response to Treatment

	AG+HC		*MPA+HC*		
No.	*All patients (Abnormal/tested)*	*Partial responders (Improved/abnormal)*	*All patients (Abnormal/tested)*	*Partial responders (Improved/abnormal)*	*P*
Bone scan	29/29	8/29	30/30	1/30	<0.02
Soft tissue	5/29	1/5	5/30	0/5	
ACP	26/29	11/26	27/30	10/27	
PAP	20/29	11/20	21/30	8/21	
ALP	29/29	12/29	30/30	6/30	
	Median (range)	Median (range)	Median (range)	Median (range)	
Pain score	60 (50–80)	50 (30–60)	60 (30–80)	70 (60–90)	<0.05
Morphine usage (mg)	60 (20–80)	40 (20–50)	60 (20–80)	75 (50–100)	<0.05
Performance status	60–69 (50–79)	60 (50–79)	60–69 (50–80)	51–59 (30–69)	<0.05
Median duration of survival (months)	10 (8–15)	11 (8–21)	5 (2–7)	—	=0.06

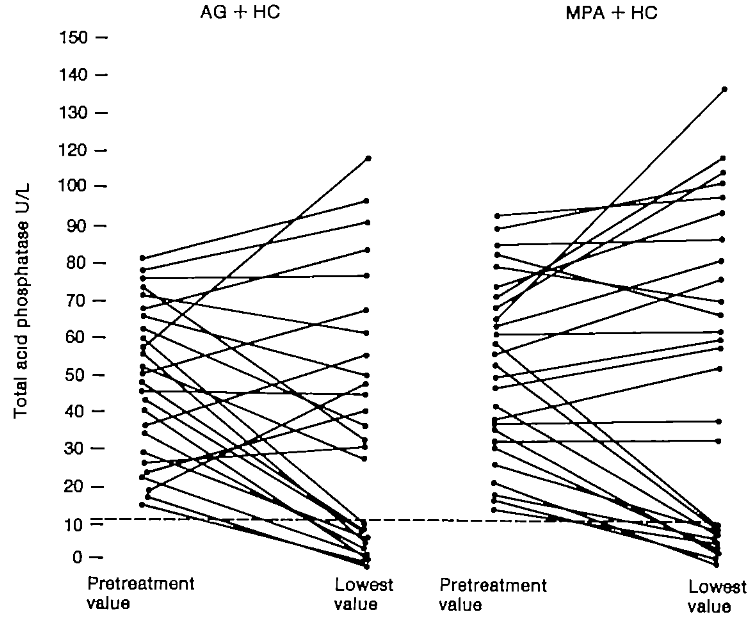

Fig. Changes in total acid phosphatase during treatment with AG + HC and MPA + HC. Baseline and lowest values The dotted line represents the upper limit of normal values.

Table 3 AG+HC Versus MPA+HC in Advanced Prostate Cancer: Adrenal Androgen Suppression

	Testosterone	Δ^4 *mmol/l*	*DHEAS*
AG+HC			
Pre-treatment	1.07±0.47	1.67±1-11	1.73±1.38
12 weeks*	0.48±0.38	0.71±0.21	0.53±0.38
	$P<0.05$	$P<0.05$	$P<0.05$
MPA+HC			
Pre-treatment	1.02±0.63	1.86±1.02	1.75±1.21
12 weeks	0.37±0.63	0.82±0.41	0.61±0.42
	$P<0.02$	$P<0.05$	$P<0.05$

* 12-week period from maximum dose AG reached. 26 patients in the AG+HC arm completed at least 12 weeks of therapy, including 19 receiving 1250 mg/day of AG and all responding patients 24 MPA+HC patients received at least 12 weeks of treatment. Hormone measurements were performed after ether extraction of plasma followed by celite chromatography and RIA.

treated with AG + HC compared with those receiving MPA+HC. At the dosages of AG used, glucocorticoid replacement was necessary and so the trial design took into account a possible glucocorticoid effect (Miller and Hinman, 1954) by the inclusion of hydrocortisone in both arms of the study. This made the 2 study arms more easily comparable and also points to the conclusion that the treatment effects seen were due to aminoglutethimide.

One rationale for the use of aminoglutethimide is to suppress adrenal androgen production as a source of androgenic stimulation in patients whose testicular production of male hormones has been effectively ablated or suppressed. Both surgical and medical castration (GnRH analogues) reduce androgen production by approximately 90%. Small amounts of androgenic steroids are produced by the adrenal glands. The importance of adrenal androgen production for tumour progression remains uncertain. Following surgical castration no

Table 4 AG+HC Versus MPA+HC in Prostate Cancer: Toxicity

	AG+HC		*MPA+HC*	
Side effects	*No.*	*(%)*	*No.*	*(%)*
Skin rash	3	(10)	0	
Oedema	0		1	(4)
Hypotension	1	(3)	0	
Hypertension	1	(3)	1	(4)
Gastrointestinal	2	(7)	2	(7)
Fever	2	(7)	1	(4)
Number of patients withdrawn because of toxic side effects	2	(7)	1	(4)

late increase in androgen production has been observed, yet disease progression occurs in the majority of patients. Two explanations have been offered for this observation. Either a hormone-insensitive clone develops or testicular androgen deprivation may eventually result in endocrine responsive cells becoming exquisitely sensitive to the low levels of androgens secreted by adrenal glands. This latter hypothesis would account for the responses to surgical adrenalectomy reported by Brendler (1973) and Mahoney and Harrison (1972). However, whether adequate adrenal androgen suppression is achieved with the use of aminoglutethimide or whether adrenal suppression following aminoglutethimide therapy is largely a steroid effect due to the replacement glucocorticoids are controversial issues which were not resolved in previous studies (Roston *et al.*, 1983; Worgul *et al.*, 1983; Block *et al.*, 1984; Ponder *et al.*, 1984; Harnet *et al.*, 1987). Plowman *et al.* (1987) found less suppression of androgenic steroids among orchiectomised patients receiving aminoglutethimide in addition to glucocorticoids than among patients receiving glucocorticoids alone. This finding was confirmed by Dowsett *et al.* (1988). It should, however, be pointed out that while adrenal suppression can be achieved with glucocorticoids alone, the duration of response of prostate cancer to glucocorticoid therapy is generally brief. Furthermore, both studies which compared the effect of hydrocortisone alone with that of hydrocortisone plus aminoglutethimide on adrenal androgen suppression used significantly lower doses of aminoglutethimide than were employed in the present investigation. This difference in dosage is relevant in view of the differential sensitivity of adrenal cytochrome P450 related enzymes and the peripheral aromatase enzyme complex. Doses of aminoglutethimide which merely cause inhibition of peripheral aromatase could result in a relative rise in androstenedione levels. To achieve a medical adrenelectomy effectively, large doses of aminoglutethimide together with replacement glucocorticoids (to avoid increased ACTH stimulation with resultant increased adrenal activity) (Santen *et al.*, 1977) would be required.

With these considerations in mind, a high dosage AG regimen was chosen for this study. Since the combination of MPA and HC also resulted in significant suppression of adrenal androgen production, but with a significantly lower objective response rate, other mechanisms of action should be considered in order to explain the results. Whether aminoglutethimide has any effect on further metabolism of androgenic steroids in prostatic tissue is at present unknown. It has also been suggested that some of the benefit from AG therapy may be due to inhibition of prostaglandin synthesis (Harris *et al.*, 1983).

Although AG+HC proved superior to MPA+HC, there were a number of patients with disease stabilisation and 1 PR using the latter regimen. The modes of action of progestogens in prostate cancer are at present unknown. In the present study, administration of MPA+HC resulted in suppression of LH and FSH levels in a significantly higher proportion of patients than did AG+HC. However, such suppression did not appear to be significant for response. Indeed the low level and short duration of response in this arm of the study may have been due mainly to HC, although Ruff *et al.* (1989) did suggest some symptomatic benefit from MPA alone. There is evidence to suggest that low levels of oestrogens are required for the maintenance of androgen receptors (Moore *et al.*, 1979). MPA, by virtue of an anti-oestrogenic effect, may interfere with cell-hormone interactions. A clearer understanding of the modes of action of these alternative and second-line hormone manipulations will emerge only from a more direct study of the cellular endocrinology of prostatic cancer rather than measurement of peripheral hormone levels.

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The Author

W. R. Bezwoda, FCP, PhD, Associate Professor and Head of Haematology/Oncology Unit.

Requests for reprints to: W. R. Bezwoda, Department of Medicine, Haematology/Oncology, University of the Witwatersrand Medical School, 7 York Road, Parktown, 2193 Johannesburg, South Africa

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Is the Penile Brachial Index a Reproducible and Useful Measurement?

M. AITCHISON, J. AITCHISON and R. CARTER

Department of Urology, Royal Infirmary, Glasgow

Summary—The intra- and inter-observer variation in the measurement of the penile brachial index (PBI) was prospectively assessed in 30 patients. An appreciable error was discovered that cast doubt on the reliability of the measurements. Up to 20% of patients deemed normal by one observer would be deemed abnormal by a second. The PBI appears to be an inaccurate and poorly reproducible test of penile blood flow which can lead to a false diagnosis and subsequent management of impotent patients. There would appear no justification for the continued use of the penile brachial index in the assessment of erectile dysfunction.

The penile brachial index, as assessed by Doppler ultrasound probe, is frequently quoted as an objective assessment of penile arterial inflow (Abelson, 1975; Van Arsdalen and Wein, 1983; Kiely and Williams, 1987) and is used in the management of impotent patients in two ways. Firstly, values below 0.6 are regarded by many authors as indicative of a vasculogenic aetiology (Kempczinski, 1979; Van Arsdalen and Wein, 1983; Abber *et al.*, 1986). Secondly, a PBI greater than 0.7 in combination with a lack of response to a papaverine injection is said to be diagnostic of venous leakage in impotence of a non-neurogenic or endocrine aetiology (Williams *et al.*, 1988).

There is no agreed standard technique for measuring the PBI in the current literature. Important variables such as cuff size, probe frequency, penile arteries measured, number of measurements made and the manner in which the value is calculated vary or are not even mentioned (Abelson, 1975; Blaivas *et al.*, 1980; Abber *et al.*, 1986; Kiely and Williams, 1987).

We found some technical difficulty in performing the measurement accurately (especially when dealing with a small penis) and when 2 observers assessed the same patient, or serial measurements were made, there appeared to be a marked discrepancy in the results. This clinical observation prompted a review of the literature which revealed that there has been no assessment of observer variation in the measurement of the PBI. The aim of this study was to determine the intra- and inter-observer error in the estimation of the penile brachial index.

Patients and Methods

The series comprised 30 men aged between 19 and 72 years. Three clinical groups were identified: 10 men with normal erectile function, 10 with significant peripheral vascular disease (5 with normal potency and 5 with erectile dysfunction) and 10 with a clinical diagnosis of psychogenic impotence.

Two observers, experienced in the vascular assessment of patients, measured the brachial and right and left arterial pressures on the dorsal surface, using an 8 MHz directional Doppler probe. A standard arm cuff and a 2.5 cm digital cuff were used for the brachial and penile pressures respectively. Cuff deflation was achieved using the built-in pneumatic system of a Medimatic SP2 plethysmograph. The instrument consists of a dual channel chart recorder, an automatic cuff inflation and

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deflation system, and a recording manometer. Measurements were performed blind to exclude observer bias.

The following method was used to calculate the PBI. The brachial systolic pressure was measured in the antecubital fossa. The arteries were then identified distal to the penile pneumatic cuff. Following cuff inflation, the reintroduction of arterial flow on deflation was announced by the observer, the value being unknown to him. If the observer was unhappy with the accuracy of the measurement, this was repeated. The procedure was then repeated on the opposite side. These measurements were repeated by both observers. The PBI was calculated as being the ratio between the highest penile pressure and the brachial pressure.

The coefficient of error for both inter- and intra-observer variation was calculated. By using log ratio analysis the combined error between and within observers was estimated. Using this combined error the lower and upper value at the 95% confidence level, between which a single measurement of the PBI might lie, was determined. The effect of repeated measurements in improving the accuracy of the PBI was evaluated.

Results

An example of the data obtained on 1 patient is shown in Table 1.

Following collation of the data from all 30 patients, the calculated coefficient of error between single serial measurements by 1 observer ranged from 0 to 23% (mean 6.2) and between 2 observers it ranged from 0 to 50% (mean 10.8). In practical terms, if an absolute value of <0.7 was taken as a diagnostic level, then 20% of patients regarded as normal by one observer would be deemed abnormal by another. Similarly, 13.3% of patients deemed normal by one observer would be regarded as abnormal by the same observer on a second measurement.

Using log ratio analysis, if a patient had a single measurement of the PBI calculated to be 0.7, the 95% confidence region would lie between 0.57 and 0.85. The effect of repeated measurements on the 95% confidence region are shown in Table 2.

Discussion

Since the late 1970s, considerable interest has focused on the value of penile pressure measurements in the assessment of impotence. Any clinical measurement should be reproducible and should have some diagnostic value to the clinician. This study has addressed the first requirement.

As with most clinical measurements, the present study has illustrated that there is a significant intra-observer error and a larger inter-observer error in the measurement of the PBI. The clinical importance of this error is that an appreciable number of patients will be assigned to different diagnostic groups by the same observer on 2 measurements or by 2 observers.

The log ratio analysis performed using the combined inter- and intra-observer error emphasises the broad range between which the value of the PBI may lie if only a single measurement is taken. Repeated measurements appear to improve the accuracy to a level which might be of clinical use. This, however, requires to be tested prospectively.

One important facet of any test is the reproducibility between centres as well as between 2 observers in the same centre. It is therefore essential that either a standard technique is applied or that a detailed methodology is included in published work.

The present study used the highest systolic pressure measured on an artery on the dorsum of the penis. Although some studies have specified values measured in particular anatomical arteries, it is difficult to determine which artery is being assessed using only a Doppler ultrasound probe (Malvar *et al.*, 1973; Blaivas *et al.*, 1980; Jevtich, 1980). Part of the appreciable error described in

Table 1 Example of Measured Values

Observers	*Brachial*	*Penile*		*PBI*
		Right	*Left*	
1a	178	130	90	0.73
1b	172	140	100	0.81
2a	180	113	117	0.65
2b	170	90	120	0.70

Table 2 Effect of Repeated Measurements

No of measurements	*95% confidence limits*	
	Lower limit	*Upper limit*
1	0.57	0.85
2	0.61	0.80
3	0.62	0.78
4	0.63	0.77

this study is probably related to the observers' inability to discriminate between the dorsal penile and cavernosal arteries. Recent work comparing the penile brachial index with duplex ultrasound and cavernosal artery occlusion pressure has shown the resting PBI to be an inaccurate test for this reason (Padma-Nathan, unpublished data).

The accuracy of the PBI as a valid clinical measurement has to be questioned following the results of this study. Absolute values below 0.6 have been quoted as indicative of a vasculogenic cause for impotence (Abelson, 1975; Van Arsdalen and Wein, 1983; Kiely and Williams, 1987). However, careful review of the literature reveals that no clear relationship has been demonstrated between any absolute value of the PBI and any specific aetiology. Although low values on repeated measurements may suggest arterial insufficiency, a higher level does not exclude it (Zorgoinotti *et al.*, 1980; Gall *et al.*, 1988).

The ratio of the penile systolic pressure to the brachial systolic pressure is an arbitrary and indirect assessment of penile arterial inflow in the resting state. The recent development of intracorporeal injection of papaverine provides a more clinically significant dynamic test of the ability of the penile vasculature to produce an erection in the absence of venous pathology

The PBI is fundamentally flawed as a diagnostic test for 2 reasons. Firstly, for the individual patient the value obtained cannot be used by the clinician to confirm or refute a vasculogenic aetiology for the erectile dysfunction. Secondly, as this study has shown, the calculated value is inaccurate. We feel that the use of the penile brachial index should be abandoned.

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The Authors

M. Aitchison, FRCS, Registrar.
J. Aitchison, DSc, FRSE, Emeritus Professor of Statistics.
R. Carter, FRCS, Registrar.

Requests for reprints to: M. Aitchison, Department of Urology, Royal Infirmary, Glasgow G4 0SF.

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Silent Testicular Metastasis from Carcinoma of the Prostate

Z. KIRKALI, R. REID, R. F. DEANE and K. F. KYLE

Departments of Urology and Pathology, Western Infirmary, Glasgow

Summary—Secondary testicular tumours are rare, but metastasis of prostatic carcinoma to the testis is being reported more frequently. While this may not reflect a true increased incidence, more cases are detected by bilateral orchiectomy. Of 916 patients with carcinoma of the prostate diagnosed and treated over a period of 10 years, 124 underwent bilateral orchiectomy. Three patients were found to have testicular metastasis, 1 being bilateral. The route of spread seems to be through the lumen and/or lymphatics of the vas deferens. Although it is a sign of advanced disease, the prognostic significance is undetermined.

Secondary testicular tumours are rare. Price and Mostofi (1957) found 38 such cases among 1600 testicular tumours; 14 of these were secondary to lung cancer and 12 were metastases from prostatic carcinoma. Semans (1938) was the first to describe metastasis of prostatic carcinoma to the testis. Nearly 70 patients with various clinical presentations were reported after publication of the first report (Johansson and Lannes, 1983; McWilliams *et al.*, 1983; Blacklock, 1984; Takahashi *et al.*, 1986; Lyngdorf and Nielsen, 1987; Moskovitz *et al.*, 1987).

We present 3 patients with carcinoma of the prostate who were found to have unsuspected metastasis to the testis discovered at therapeutic bilateral orchiectomy. The possible aetiological mechanisms of such spread are discussed.

Patients and Methods

All patients with histologically proven carcinoma of the prostate diagnosed and treated in the Western Infirmary over a 10-year period were reviewed. Formal or subcapsular orchiectomy was performed in patients with locally advanced and/or metastatic disease (a) as a primary mode of treatment, (b) as alternative treatment in those who failed to respond or who could not tolerate antiandrogenic and/or hormonal treatment and (c) in combination with other forms of therapy.

Tissue samples obtained by transurethral resection or transrectal biopsy of the prostate and orchiectomy specimens were fixed in formalin and stained with haematoxylin and eosin. The slides from patients with metastatic spread of prostatic cancer were reviewed; other serial sections were taken and also stained with antisera to prostatic acid phosphatase (PAP) and prostate specific antigen (PSA) by the immunoperoxidase technique.

Case Reports

Case 1. A 75-year-old man who presented with acute retention of urine underwent surgery. Histology revealed carcinoma of the prostate (Gleason grade 3). Two years later he was readmitted with obstructive symptoms and a repeat resection and bilateral orchiectomy were performed. Pathological examination showed metastasis to the left testis. He later developed multiple bone and retinal metastases and received palliative radiotherapy. He died of metastatic disease 4 years after the initial diagnosis.

Case 2. A 61-year-old man presented with acute retention of urine and was found to have carcinoma of the prostate (Gleason grade 4). He was put on diethylstilboestrol 5 mg daily for extensive bone metastasis. He developed deep

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vein thrombosis, pulmonary embolism and myocardial infarction 1 month after starting treatment. Bilateral orchiectomy was performed after his medication was stopped. Histology revealed bilateral testicular metastasis of prostatic carcinoma. Despite a subjective response of 4 months' duration, his disease progressed and he died of metastatic disease 3 years after diagnosis.

Case 3. A 79-year-old man, who had previously undergone prostatectomy for benign disease, developed obstructive symptoms. Needle biopsy confirmed the diagnosis of prostatic carcinoma (Gleason grade 3) and bilateral orchiectomy was performed. Histology revealed metastatic carcinoma of the prostate in the right testis. The patient is alive and has normal PAP levels 4 years after diagnosis.

Results

The series comprised 916 patients diagnosed and treated for carcinoma of the prostate; 124 (13.5%) were treated by bilateral orchiectomy either initially or during the course of their disease. Three patients who underwent therapeutic bilateral orchiectomy had testicular metastasis (2.4%), 1 being bilateral. None of the patients had symptoms or signs related to their testicular metastasis.

Histological examination in Case 1 showed a deposit of metastatic carcinoma within the interstitium of the testis confirmed by positive staining for PSA and PAP (Fig. 1). Several small foci of tumour were identified in the epididymis and appeared to have replaced the epithelium of the epididymal tubules. In Case 2, both testes contained multiple deposits of haemorrhagic, focally necrotic lesions, particularly near the testicular hilum. Histological examination showed tumour in the rete testis and widely distributed within seminiferous tubules; this was confirmed by elastic staining (Fig. 2). Case 3 also had PSA and PAP positive metastatic carcinoma mainly in the interstitium of the right testis.

Discussion

Carcinoma of the prostate is the second most common tumour in males after lung cancer (Cancer Registration Statistics Scotland, 1984). It is known to metastasise to various tissues, but mainly to lymph nodes, bones, liver and lungs. Although testicular spread of prostatic cancer is rare, it is being reported more frequently (Takahashi *et al.*, 1986; Lyngdorf and Nielsen, 1987; Moskovitz *et al.*, 1987). Johansson and Lannes (1983) found testicular metastasis in 4% of their therapeutic orchiectomy series of 80 patients. Moskovitz *et al.* (1987) reported 1 of 56 patients who underwent orchiectomy for carcinoma of the prostate during a 5-year period. Our figure (2.4%) is similar to those and shows that a certain percentage of prostatic cancer patients have metastasis to the testis. There

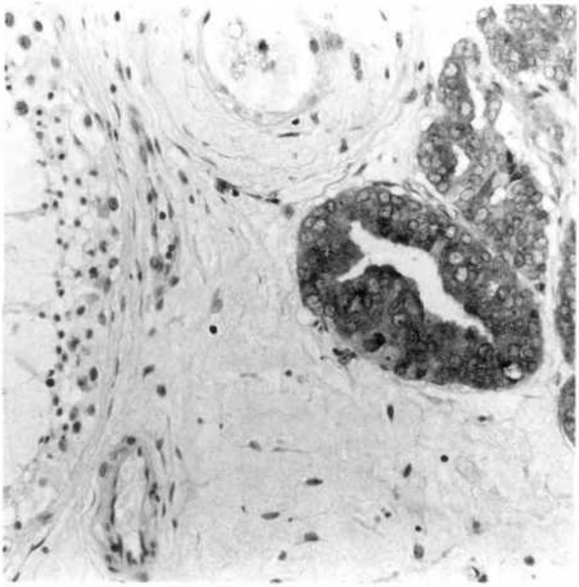

Fig. 1 Metastatic carcinoma in the interstitium of testis staining positively for PAP (Case 1). A seminiferous tubule showing some spermatogenesis and an atrophic tubule are present. (PAP × 250).

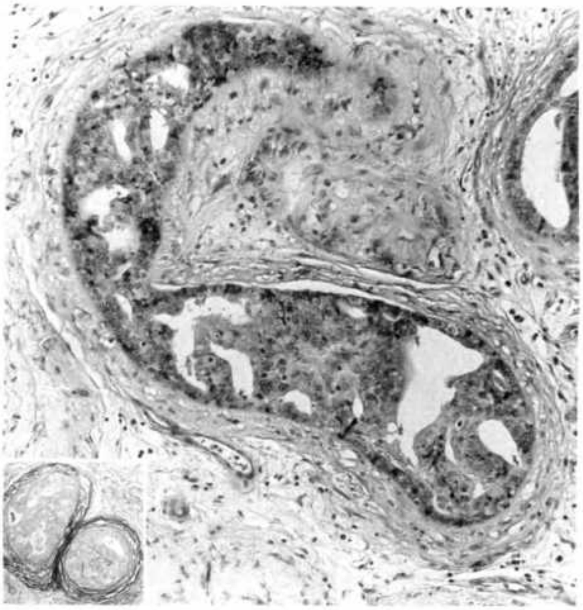

Fig. 2 Intratubular spread of carcinoma of cribriform pattern in Case 2. (H–E × 100). Inset: Intratubular spread shown by peritubular elastic tissue staining. (Elastica Van Gieson × 100).

are often no symptoms or signs of this spread and the diagnosis can be made only by histological examination of the orchiectomy specimen or at post mortem examination. More surgical castration in the form of formal orchiectomy will increase the chances of detecting testicular, epididymal and spermatic cord metastasis from carcinoma of the prostate.

There are 5 possible routes by which prostatic cancer spreads to the testis: (a) arterial embolism, (b) retrograde venous extension, (c) retrograde lymphatic spread, (d) direct extension and (e) through the lumen of the vas.

Arterial embolism is unlikely because it is not a major route of spread in prostatic carcinoma and, in addition, there are patients with solitary metastasis to the testis (Johansson and Lannes, 1983; Blacklock, 1984). It is also difficult to explain the occurrence of similar bilateral metastases in the testes. Retrograde venous extension is a probable mechanism, and increased intrapelvic pressure may initiate retrograde flow to the testis. A similar mechanism of metastasis to the bones and the presence of tumour nodules in the spermatic cord in some cases supports this theory (Johansson and Lannes, 1983).

Hanash *et al.* (1969) suggested that the route of metastatic testicular tumours from the prostate gland was via the lumen or lymphatics of the vas deferens. Reports of patients with metastasis to the testis, in the absence of widespread disease, strongly support this theory (Johansson and Lannes, 1983; Blacklock, 1984). The presence of nodules in the spermatic cord may be a sign of lymphatic spread. Intratubular tumour within the vas deferens shows that the route is through the lumen of the vas deferens (Johansson and Lannes, 1983). This appears to be the most widely accepted explanation (Kay *et al.*, 1954; Marble, 1960). We took serial sections from the spermatic cord and could not detect any tumour either within the lumen of the vas or in the spermatic cord.

Duchek and Winblad (1973) showed that tuberculosis of the intrascrotal contents is the end result of retrograde lymphatic spread and this probably holds true for the spread of prostatic carcinoma. Epididymal metastasis from carcinoma of the prostate in a patient who previously underwent pelvic lymphadenectomy also supports this view (Bahnson *et al.*, 1985).

Whatever the route of spread to the testis may be, it is accepted as a sign of advanced disease (Johansson and Lannes, 1983; Moskovitz *et al.*, 1987). It is usually accompanied by multiple metastases in other organs, but occasionally it is confined to the testis. Furthermore, as in 1 of our patients, survival is unaffected by this metastatic focus. The prognostic significance of testicular metastasis from carcinoma of the prostate is unknown.

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The Authors

Z. Kirkali, MD, formerly Honorary Registrar, Department of Urology, Western Infirmary. Now Associate Professor, Izmir, Turkey.

R Reid, MRCPath, Honorary Senior Registrar, Department of Pathology

R. F. Deane, FRCS, Consultant Urologist.

K. F Kyle, FRCS, Consultant Urologist.

Requests for reprints to· Z Kirkali, Department of Urology, Dokuz Eylul University School of Medicine, Inciraltı, Izmir, Turkey 35340.

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Relationship of Primary Site of Testis to Final Testicular Size in Cryptorchid Patients

P. PURI and A. SPARNON

Children's Research Centre, Our Lady's Hospital for Sick Children, Dublin, Ireland

Summary—Testicular volume was examined in men who had undergone orchiopexy at or after 7 years of age; 159 men with 187 cryptorchid testes were available for estimation. The mean age at orchiopexy was 9.8 years (range 7–13.6) and the mean age at follow-up was 24.3 years (range 18–41). The data showed that surgically treated cryptorchism was associated with testes that are significantly smaller than normal. The most important factor in relation to subsequent testicular size was whether or not the testes were palpable. Testes found in the superficial inguinal pouch were approximately 85% of normal testicular volume. Contralateral testicular volume in unilaterally cryptorchid patients was not significantly different from that of controls.

Cryptorchism is now the most common disorder in children requiring elective surgery. The fertility status of cryptorchid patients remains a controversial subject. Numerous histological studies have revealed that pathological features begin to appear in the cryptorchid testis at an early age and become more pronounced by the second year of life (Mengal *et al.*, 1974; Hedinger, 1982). It has also been reported that most patients with unilateral cryptorchism show evidence of abnormal morphological changes in the contralateral scrotal testis (Shirai *et al.*, 1966; Hedinger, 1979; Hadziselimovic, 1983). For these reasons it has been recommended that orchiopexy should be performed as early as possible, probably late in the first year, in order to preserve subsequent fertility (Hadziselimovic, 1982; Kogan, 1988). However, the outcome in terms of fertility has not been evaluated adequately by follow-up.

The results of semen analysis were reported in men who had undergone orchiopexy for cryptorchism at or after 7 years of age; the important factors in predicting fertility were whether the condition was unilateral or bilateral and whether or not the testes were palpable (Puri and O'Donnell, 1988).

Since the bulk of the testis is composed of seminiferous tubules, measurement of testicular volume has been used to estimate tubular function and a positive correlation has been reported between testicular size and spermatogenesis (Sherins *et al.*, 1978; Comhaire *et al.*, 1987; Takihara *et al.*, 1987). No data are available on testicular volume in men operated on for cryptorchism in childhood. This report presents data on testicular volume in men who underwent orchiopexy at or after 7 years of age.

Patients and Methods

During a 19-year period (1957–1975), 511 boys with cryptorchism were treated by orchiopexy at Our Lady's Hospital for Sick Children, Dublin. Of these patients, 329 who had undergone orchiopexy between the ages of 7 and 13.5 years of age were now over the age of 18 years. They were contacted by means of a questionnaire which sought information on marriage, paternity and willingness to attend for a personal interview and examination.

A total of 234 men (71%) returned the questionnaire, 28 of whom were now living abroad; 159 attended for interview and examination. Testicular volume was determined using Prader's orchiometer (Prader, 1966). The device consists of 12 models of a defined shape (rotation ellipsoids) with volumes of 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 20 and 25 ml. Each

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testis was palpated with one hand while the model testis was palpated with the other hand and the sizes compared; 20 normal adults (age range 18–23 years) with 40 scrotal testes acted as controls.

Statistical analysis

The mean and 1 standard deviation were calculated for testicular volumes observed in cryptorchid testes and controls. Student's *t* test was used for statistical comparisons.

Results

Testicular volume was assessed in 159 men. Their mean age at orchiopexy was 9·8 years (range 7–13.6) and the mean age at follow-up was 24.3 years (range 18–41); 131 men had unilateral and 28 had bilateral cryptorchism. Table 1 shows the primary anatomical position of 187 cryptorchid testes. Surgical exploration in 13 of these testes had disclosed an absent or vanishing testis; testicular volume was estimated in the remaining 174 testes. Their final position at follow-up was scrotal in 148, high scrotal in 14 and inguinal in 5; 7 men either showed no evidence of testis or had severe testicular atrophy, with the testicular volume measuring less than 1 ml. There was a significant reduction in testicular volume in abdominal, canalicular and superficial inguinal pouch testes when compared with controls ($P<0.0001$) (Table 2). The mean testicular volume of superficial inguinal pouch testes was over 3 times greater than the mean testicular volume of abdominal testes and nearly twice that of canalicular testes. The contralateral testicular volume in 131 unilaterally cryptorchid patients was not significantly different from that of controls ($P>0.05$).

Discussion

Measurement of testicular volume is an approximation and can be affected by shape, relationship of the epididymis to the testis, layers of scrotal skin and the possibility of compression of the tissues (Daniel *et al.*, 1982). We found Prader's orchiometer to be the most satisfactory method of estimating testicular volume. The procedure is fast and easy and causes less apprehension and undesirable manipulation of genitalia than any other method, such as measurement of testicular length and width with callipers.

Table 1 Primary Anatomical Position of 187 Cryptorchid Testes*

Site	*No*
Intra-abdominal	19
Inguinal canal	36
Superficial inguinal pouch	119

* Surgical exploration in 13 cases disclosed an absent or vanishing testis

Table 2 Testicular Volume

	Testicular volume (ml)		
Primary site of testis	*Range*	*Mean ± 1 SD*	*P*
Abdominal (n = 19)	0–10	4.9±3.5	<0.0001
Inguinal canal (n = 36)	0–20	9.8±4.4	<0.0001
Sup ing pouch (n = 119)	2–25	17.0±4.9	<0.0001
Contralateral testis in unilateral cases (n = 131)	3–25	21.1±4.4	N S *
Normal controls (n = 40)	8–25	20.8±4.3	—

* N S = Not significant.

It is generally believed that testicular size is the best primary assessment of spermatogenesis, since the tubules and germinal elements account for approximately 98% of the testicular mass (Takihara *et al.*, 1987). A decrease in the number of germ cells leads to testicular hypoplasia and satisfactory spermatogenesis is presumed to be possible only in a testis of normal or near normal size. This study has shown that surgically treated cryptorchism is associated with testes that are significantly smaller than normal. The most important factor in relation to subsequent testicular size was whether or not the testes were palpable. Those found in the superficial inguinal pouch were approximately 85% of normal testicular volume. On the other hand, intra-abdominal and intra-canalicular testes were significantly smaller than superficial inguinal pouch testes. This could be explained by the fact that high testes are more difficult to bring down and atrophy is more likely. It is also possible that the smaller size may be due to the cryptorchism itself. It may be argued that orchiopexy performed on children less than 2 years of age may reduce the incidence of subsequent testicular disease. Since the policy of earlier orchiopexy is relatively new, no follow-up studies are yet available.

Several authors have reported abnormal numbers of germ cells in the contralateral descended testis in unilateral cryptorchism (Shirai *et al.*, 1966; Hedinger, 1979). In the present study the contralateral testicular volume in unilaterally cryptorchid patients was normal, indicating that fertility should be good. These observations are further supported by our earlier findings on semen analysis which showed that men who had unilateral cryptorchism produced normal semen after orchiopexy (Puri and O'Donnell, 1988).

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The Authors

P. Puri, MS, FACS, Director of Research.
A Sparnon, FRACS, Senior Registrar in Paediatric Surgery

Requests for reprints to · P. Puri, Children's Research Centre, Our Lady's Hospital for Sick Children, Crumlin, Dublin 12, Ireland.

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The Long-term Outcome following "Special Clearance" after Vasectomy

A. H. DAVIES, R. J. SHARP, D. CRANSTON and R. G. MITCHELL

Elliot Smith Clinic, Churchill Hospital, Oxford

Summary—Between 1980 and 1985, 6067 out-patient vasectomies were performed under local anaesthesia at the Elliot Smith Clinic in Oxford. During this period 151 men (2.5%) were given a "special clearance". This sanctioned the discontinuation of other forms of contraception despite the persistence of scanty (< 10,000/ml) sperm in 2 consecutively examined semen samples at least 7 months after vasectomy. These men have been reviewed and further specimens of semen requested after a minimum follow-up of 3 years (range 3–8); 50 patients supplied a specimen and all except 1 were azoospermic. No pregnancies attributable to failure of the vasectomy have been identified.

Previous reports have shown vasectomy to be a procedure which is safe, simple and has few complications and failures (Population Reports, 1983; Philp *et al.*, 1984a). It is well recognised that a few patients continue to pass low numbers of sperm in their semen for many months. The normal criterion for sterility in this clinic consists of 2 consecutive azoospermic analyses at least 4 months after vasectomy, further samples being examined until this is achieved. However, men with persistently positive semen samples are given a "special clearance" if 2 consecutively examined specimens have counts < 10,000/ml and at least 7 months have elapsed since vasectomy. The outcome in this group has been the subject of debate (Barnes *et al.*, 1973).

Patients and Methods

Between 1980 and 1985, 6067 men underwent vasectomy under local anaesthesia at the Elliot Smith Clinic. In almost all cases Hyfrecator cautery was applied to the ends of the divided vas; 151 men (2.5%) were given a "special clearance" as described above. The mean age of this group was 40 years (range 27–66). The mean age of a random group of 151 consecutive men attending the clinic for vasectomy was 36 years (range 26–59). Men who were given a special clearance received a letter which stated that in the experience of this clinic and others worldwide no pregnancies had occurred to date by adopting this policy and that other methods of family planning could now be discontinued. However, it was stressed that no guarantee could be given that a vasectomy would not fail at any point in the future.

A letter and specimen container with a request to provide a further semen sample for analysis were sent to the 151 patients. If no reply was obtained the patient's last known family doctor was contacted for information.

Results

A total of 151 men (2.5%) were given a special clearance. The minimum time at follow-up from clearance was 3 years.

Table 1 summarises the results *per annum*; 52 patients (34%) replied, of whom 50 (33%) supplied a further specimen and 2 declined to participate. All but 1 were found to be azoospermic. The exception was a man aged 50 at the time of his vasectomy 5 years previously. His semen specimen contained < 5,000 sperms/ml.

The reply rate correlated with the year of vasectomy; only 16% of the 1980 patients replied, whereas 48% of the 1985 patients replied; 14 containers (9%) were returned unopened by the Post Office.

The family doctors of the 99 who failed to reply were contacted. Table 2 shows the outcome and the reasons for no reply; only 17% were still at the same address.

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Table 1 Results *per annum*

Year	*No. of vasectomies*	*Special clearance* *No.*	*(%)*	*Replies* *No*	*(%)*
1980	1010	38	(4)	6	(16)
1981	967	28	(3)	9	(32)
1982	888	16	(2)	6	(38)
1983	899	17	(2)	6	(35)
1984	1159	19	(2)	9	(47)
1985	1144	33	(3)	16	(48)
Total	6067	151	(2.5)	50	(33)

In this group of 151 patients no subsequent complications and no pregnancies were reported.

Discussion

Our policy of special clearance resulted in azoospermia at long-term follow-up in 98% of patients and the single exception had only a "few scanty sperms" present. No evidence was obtained from either patients or family doctors of the occurrence of pregnancies or morbidity. Persistence of sperm after vasectomy may result from inadequate vasectomy, early recanalisation (Barnes *et al.*, 1973; Rees, 1973; Philp *et al.*, 1984a), late recanalisation (Philp *et al.*, 1984b) or residual sperm stored distal to the site of the vasectomy. The 34% reply rate appears low, but it represents 60% of the men who had not moved house and was inversely related to the number of years since vasectomy. We considered that non-response should be regarded as a decision not to participate on the part of the 17% of patients known to be at the same address. In the study group 98% became azoospermic. Freund and Davies (1969) stated that 10 ejaculates were necessary for clearance, whereas Marshall and Lyon (1972) showed that 36 ejaculates would be necessary for 100% clearance. Our findings suggest that delayed clearance represents exceptionally slow distal emptying. The study group was rather older than a consecutive group of men undergoing vasectomy. Marshall and Lyon (1972) showed that younger patients had more ejaculates and postulated that ejaculatory peristalsis is more vigorous in the young, while Spencer and Charlesworth (1976) showed a decreased rate of clearance with age irrespective of coital frequency. We consider that our retrospective data support the view of Edwards and Farlow (1979) who advocated that clearance on the basis of scanty sperms did not lead to a risk of pregnancy. However, this is contrary to the view of Jackson (1973) that repeated tests should be performed until azoospermia is complete. Our one case of a few scanty non-motile sperm 5 years after vasectomy does not suggest late recanalisation (Philp *et al.*, 1984b). An alternative explanation is that the vasectomy nodule in special clearance cases permits a few sperms to pass through its channels; these are non-motile and incapable of causing conception.

Table 2 Results of Attempted Telephone Contact with Family Doctors

	No	*(%)*
Unable to trace doctor	17	(17)
Moved and changed doctor	65	(66)
Same address	17	(17)

These results are reassuring for patients issued with a special clearance. They may be told that their chance of being fertile is minimal rather than zero and made aware that any vasectomy may fail at a future date.

Acknowledgements

We thank Messrs J Guillebaud and I MacKenzie, Clinic Surgeons, Sisters E Turner and P Ashcroft and the other staff of the Elliot Smith Clinic for their help.

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The Authors

A. H. Davies, FRCS, Registrar in Urology.
R J. Sharp, BA, Medical Student.
D Cranston, FRCS, Clinic Surgeon.
R. G Mitchell, FRCPath, Consultant Microbiologist.

Requests for reprints to: A H Davies, Department of Urology, Churchill Hospital, Headington, Oxford OX3 7LJ.

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Case Reports

Unusual Complication of Spongiosium-cavernosum Shunt in the Treatment of Priapism: Bilateral Diverticuli of Corpus Cavernosum

S. KÜPELI, N. ARIKAN, K. AYDOS and G. KARALEZLI,
Department of Urology, Hospital Ibni Sina (Avicenna), Ankara University, Ankara, Turkey

Case Report

A 41-year-old man was referred with a 6-month history of unresolved priapism and the formation of 2 bulbs located on the dorsolateral aspect of the middle of the penis.

He had been referred initially to another medical centre 3 days after the onset of priapism, when needle aspiration and irrigation through the dorsum of the glans penis resulted in immediate detumescence but approximately 18 h later, priapism recurred. Six days after this initial intervention a spongiosum-cavernosum shunt was performed in the same medical centre.

Approximately 45 days after the shunt, he observed bilateral painless, soft swellings on the dorsolateral aspect of the middle of the penis on the incision sites.

Physical examination of the external genitalia revealed an enormous penis. The glans penis, scrotum and testes were normal. On the dorsolateral aspect of the middle of the penis were bilateral painless, soft, homogeneous bulbs on the previous shunt incisions (Fig. 1).

Urine analysis, complete blood count, haemoglobin electrophoresis and serum chemistry studies were all normal. At arteriography of the internal pudendal artery no evidence could be obtained to show the aetiological factors. At cavernosography the penile swellings opacified and were seen as diverticulum-like formations with strictly defined contours (Fig. 2).

Comment

In priapism the most significant complication is impotence, which occurs in 50% of patients regardless of treatment (Winter and McDowell, 1988).

Less common complications following a spongiosum-cavernosum shunt include urethrocavernous fistula (Robbins *et al.*, 1984), necrosis, gangrene, chronic engorgement and diverticulum-like formations on the penis. Thrombosis, fibrosis and recurrent priapism may also occur (Winter and McDowell, 1988).

In our case, the bilateral bulbs were shown to be

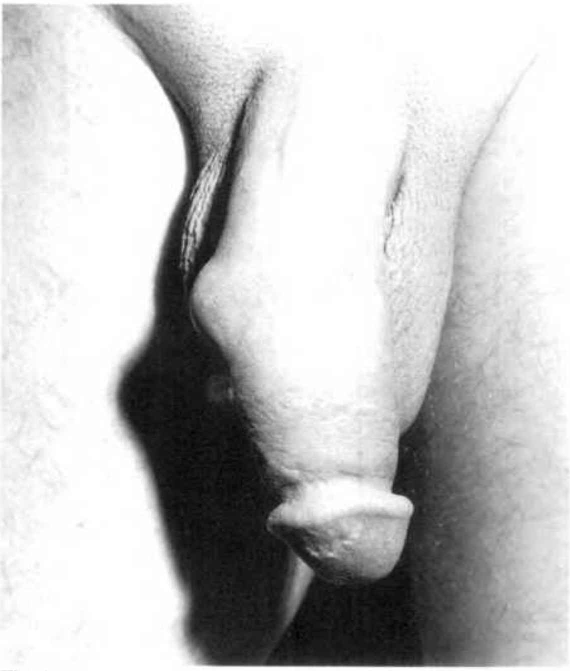

Fig. 1

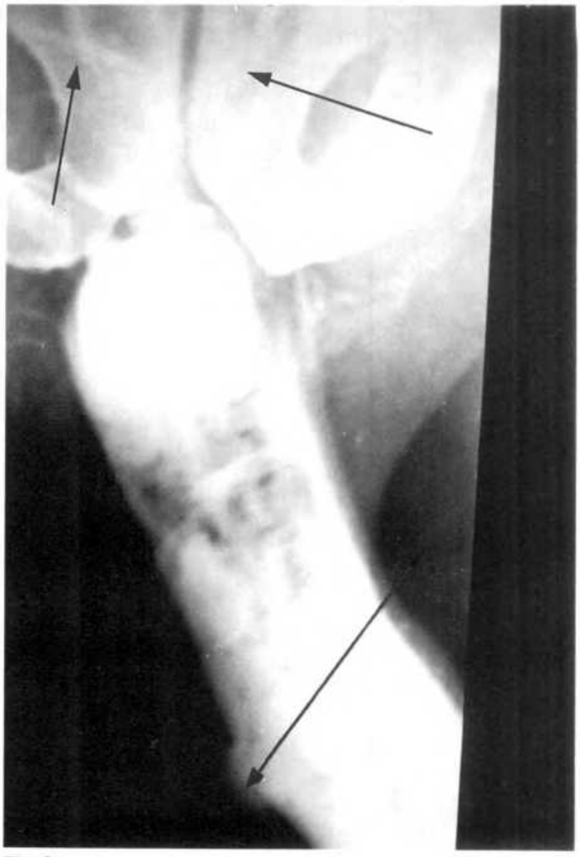

Fig. 2

diverticulum-like formations of the corpus cavernosum.

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Requests for reprints to: S. Küpeli, Ankara Üniversitesi, Ibni Sina Hastanesi, Üroloji Servisi Sihhiye, Ankara, Turkey.

Skin Bridge—A Complication of Paediatric Circumcision

U. V. SATHAYE, A. K. GOSWAMI and S. K. SHARMA, *Department of Urology, Postgraduate Institute of Medical Education and Research, Chandigarh, India*

Circumcision is a commonly performed operation in childhood. Although a minor procedure, the incidence of complications ranges from 1.5 to 5%. We report a case of "skin bridge" following circumcision.

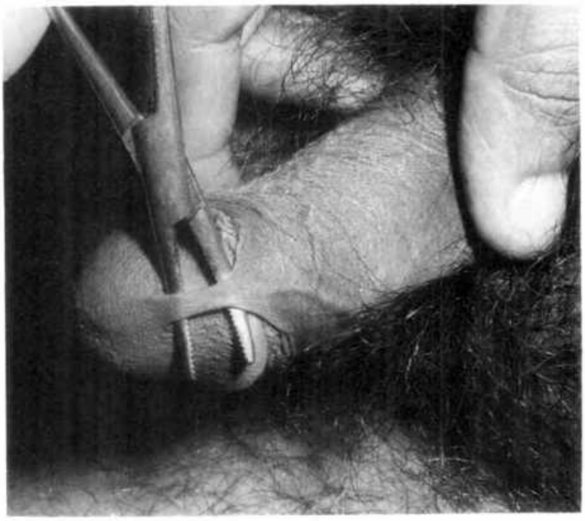
Case Report

A 29-year-old man presented with incomplete erection and pain in the penis of 6 months' duration. Examination revealed a skin bridge extending from the middle of the glans to the prepuce on the dorsal aspect, just to the right of the midline (Fig.). Except at the points of attachment, the band was otherwise free and well formed. It was lax and could be stretched without pain. The patient had been circumcised in childhood. The band was excised with relief of symptoms.

Comment

Skin bridge is a rare cutaneous complication of circumcision and can cause tethering of the penis, entrapment of smegma, curvature of the penis and pain upon erection. The bridge can be small and may require simple surgical excision or it can be complex and require a plastic procedure.

These bridges probably originate from inadequate separation of the inner preputial epithelium from the glans at the time of circumcision (Kaplan, 1983). This results in a firm fusion of skin, inner preputial epithelium and glans and when separation does occur, a skin bridge remains (Gearhart, 1986).



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Requests for reprints to: A. K. Goswami, Department of Urology, Postgraduate Institute of Medical Education and Research, Chandigarh 160 012, India.

Giant Ureterocele—a Rare Presentation

P. G. BUDNY and F. A. W. SCHWEITZER, *Department of Urology, Royal Surrey County Hospital, Guildford*

Case Report

A 2-year-old boy, of full term and normal delivery, noted to have bilateral undescended testes at neonatal examinations, was admitted for elective orchiopexy. Symptomatically well in all respects, with normal weight gain, his mother noted he preferred fluids to solids and his umbilicus had gradually become more protuberant. Examination showed a restless, well nourished child, with testes at the superficial inguinal ring bilaterally and an apparently normal abdomen.

Right orchiopexy was performed in July 1987; the testis was rudimentary, widely separated from the epididymis and there was no vas deferens. Coincidentally, a lower abdominal mass was noted which remained unchanged after urethral catheterisation.

Subsequent ultrasound, IVU (Fig. 1), cystography (Fig. 2) and DTPA/DMSA scans demonstrated a right-sided giant simple ureterocele, megaloureter and non-functioning kidney. The left kidney and upper tract were normal, as were MSU, blood count, serum creatinine and karyotyping. In November 1987 a nephrourectomy and excision of ureterocele were performed, the kidney being "hypoplastic". Awaiting left orchiopexy, the boy remains well.

Comment

Ureteroceles are rare congenital anomalies thought to be consequent on obstructed communication between the ureteric bud of the Wolffian duct and the urogenital sinus following incomplete absorption of Chwalla's membrane. Abnormal testicular descent from the urogenital ridge is a much more common clinical problem.

It is generally agreed that urinary tract infection and its sequelae are the commonest forms of presentation of ureteroceles, with other urological symptoms, abdominal pain and masses being less frequent (Campbell, 1951; Malek *et al.*, 1972; Assadi *et al.*, 1984). A definite association with other urogenital abnormalities exists, but an association with undescended testes was not found by Campbell (1951) in his extensive experience, though Malek *et al.* (1972) referred to a single case without presenting details. As far as we are aware, this is the only specific report of such a patient.

Infants and children are difficult to examine adequately at the bedside and we suggest that abdominal examination under anaesthesia at the time of orchiopexy may occasionally be rewarded by the discovery of unexpected pathology before serious sequelae intervene.

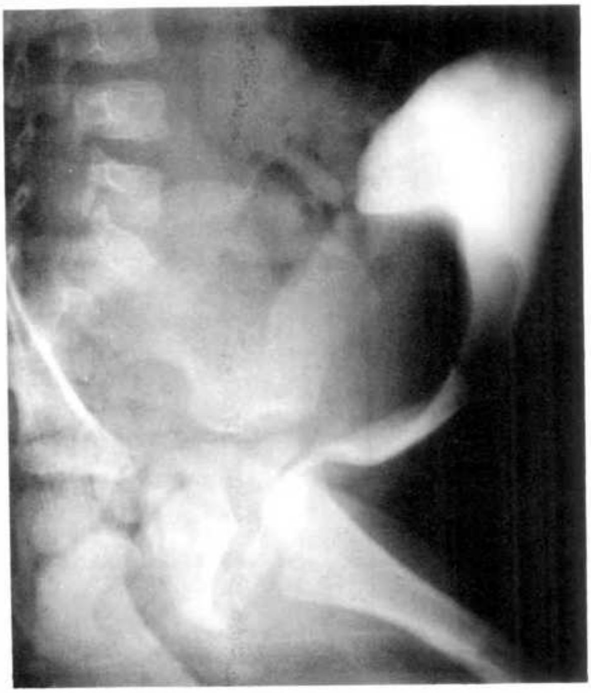

Fig. 2 Cystogram showing giant ureterocele displacing the bladder antero-superiorly.

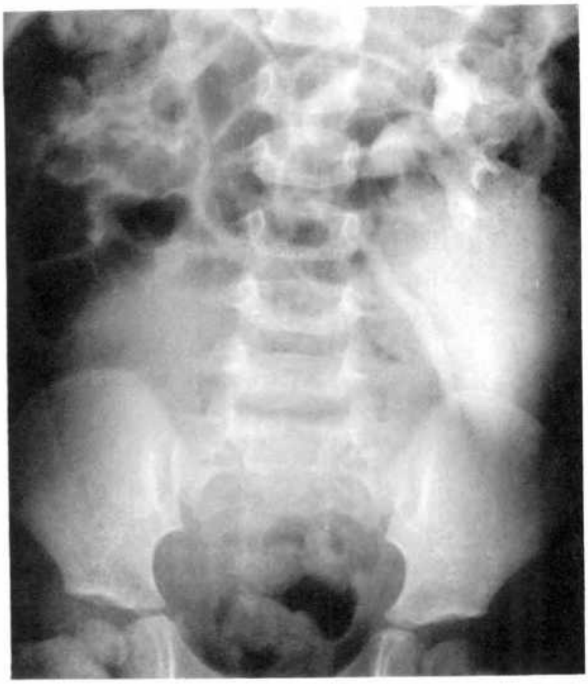

Fig. 1 IVU showing non-functioning right upper urinary tract with gross bladder displacement.

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Requests for reprints to: P. G. Budney, Department of Urology, Royal Surrey County Hospital, Guildford, Surrey.

Coincidental Renal Angiomyolipoma and Urothelial Carcinoma of the Renal Pelvis in the Same Kidney Diagnosed by CT

F. G. VEIGA, J. R. VARELA, V. CHANTADA and M. G. MARTIN, *Department of Urology, Juan Canalejo Hospital, La Coruña, Spain*

We report a case of coincidental angiomyolipoma and urothelial carcinoma of the renal pelvis in the same kidney. This association has not been reported previously.

Case Report

A 71-year-old female was admitted in 1987 with pain in the right side of the abdomen and gross haematuria. Physical examination revealed no abnormalities. Laboratory and cytology studies were normal.

CT (Fig. 1) showed a tumour with fat and soft tissue density in the right kidney. Following intravenous injection of contrast medium, the soft tissue component enhanced. A second soft tissue mass, inhomogeneous, was found in the renal pelvis in the same kidney (Fig. 2).

A right nephroureterectomy and partial cystectomy around the bladder cuff were performed. Pathological examination showed 2 masses: a typical urothelial carcinoma from the renal pelvis grade III, stage B, and an angiomyolipoma in the upper pole.

The patient is alive 18 months later.

Comment

Renal angiomyolipoma is an uncommon benign neoplasm composed of fat intermixed with blood vessels and smooth muscle. The incidence is about 2% of all renal neoplasms (Govaerts *et al.*, 1987). Urothelial carcinoma of the renal pelvis is more frequent, with an incidence of 15% (Yokoyama *et al.*, 1981).

In this case is seen an exceptional association of 2 renal neoplasms of dissimilar histogenesis occurring in the same kidney. Eleven cases of angiomyolipoma and renal cell carcinoma have been reported (Ueda *et al.*, 1987) and also 1 case of the simultaneous occurrence of renal carcinoma with urothelial carcinoma and a hamartoma in the same kidney (Yokoyama *et al.*, 1981).

This development and refinement of CT have revolutionised the diagnostic evaluation of patients with renal masses. CT has been reported to be extremely accurate in the diagnosis of angiomyolipoma because the fat content of the tumour can be recognised (Ueda *et al.*, 1987). We suggest that CT be used to discriminate rena angiomyolipoma from other renal tumours.

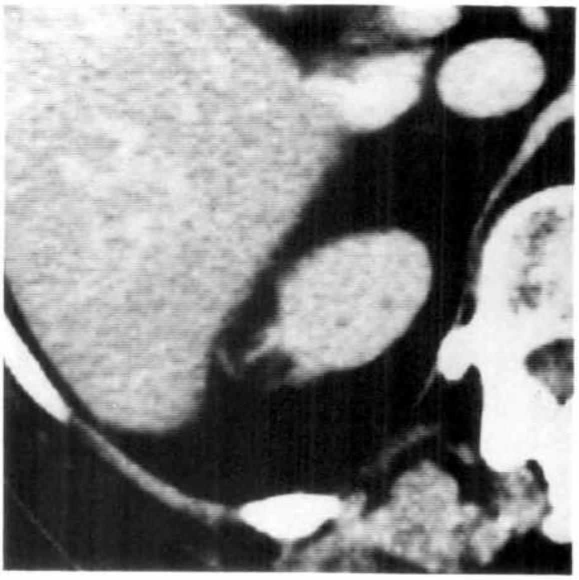

Fig. 1 CT scan showing fat density within the lesion.

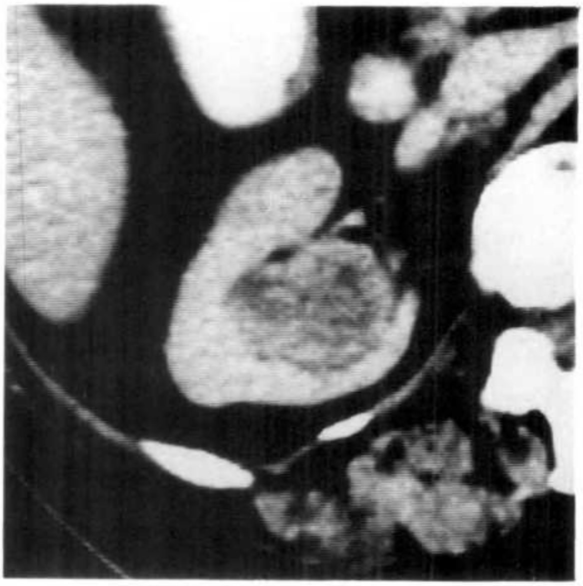

Fig. 2 CT scan showing soft tissue with compression or displacement of the renal pelvis.

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Requests for reprints to: F G. Veiga, Department of Urology, Juan Canalejo Hospital, Las Jubias 84, La Coruña, Spain.

Transverse Testicular Ectopia Presenting as Strangulated Inguinal Hernia

A. J. DICKINSON and P. HEWETT, *Department of Surgery, Royal United Hospital, Bath*

Crossed testicular ectopia is a rare but well recognised entity that usually presents in childhood (mean age 4 years) (Gauderer *et al.*, 1982). We report a case of transverse testicular ectopia in a man of 62 years.

Case Report

A 62-year-old man was admitted as an emergency with a 24-h history of a painful lump in the left groin. He gave no history of previous surgery or of pain, swelling or scrotal trauma. He was married with 1 child.

Examination revealed a tender, 5-cm irreducible swelling in the left inguinal region No cough impulse was elicited. The left testis was lying normally but the right side of the scrotum was empty and the right inguinal region was normal to palpation.

A clinical diagnosis of strangulated hernia was made and urgent exploration was undertaken through a left inguinal incision. At operation an indirect inguinal hernia was found. The hernial sac contained a 1.5-cm testis with identifiable vessels and vas deferens. Normal cord structures, including the vas deferens and testicular vessels, were also seen emerging from the left internal ring and passing to a normal left testis.

The ectopic testis was removed from the hernial sac and excised A routine hernia repair was performed. Histologically the specimen revealed a normal vas deferens and epididymis. The testis showed complete hyaline fibrosis of the tubules consistent with long-standing cryptorchidism. Chromosome analysis revealed a normal male karyotype (46XY).

Comment

Halstead (1907) first reported a case of transverse testicular ectopia and fewer than 100 cases have since been described (Gauderer *et al.*, 1982). The condition characteristically presents as a hernia on the same side as a fully descended testis and an impalpable contralateral testis (Beasley and Auldist, 1985).

Although transverse testicular ectopia usually presents in childhood, 2 previous cases were reported by Golladay and Redman (1982) in elderly men as an incidental finding at post mortem. The present case represents the first diagnosed during life in that age group. It is unusual in that it presented as an emergency and also that the testes were not identical in size. Although rare, the condition should be considered when exploring a hernia when the contralateral testis is absent.

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Requests for reprints to: A. J Dickinson, Department of Surgery, Royal United Hospital, Combe Park, Bath BA1 3NG

Superglue in the Urethra

W. H TURNER, *Department of Urology, Churchill Hospital, Oxford*

Case Report

A 22-year-old man presented, having instilled superglue into his urethra. He claimed to have thought that it was lignocaine gel, which he used occasionally for urethral pain. He was considered a hypospadias cripple because since the age of 2 he had undergone numerous operations on his penis and urethra for hypospadias. These left him with persistent pain and an unsatisfactory cosmetic and functional result. He developed psychological problems which, coupled with his low IQ, made him a management problem to the Departments of Urology, Plastic Surgery and Psychiatry. He had presented previously with lacerations to his penis, claimed to have been sustained jumping over a barbed wire fence but suspected to have been self-inflicted

At this presentation he underwent an examination under anaesthesia in the Department of Plastic Surgery and a 7-cm cast of superglue was removed from his penile urethra. It was thought that a fragment had been pushed into his bladder and he was referred to the Department of Urology for panendoscopy.

Under general anaesthesia he was found to have a further 2-cm fragment in the posterior urethra, loosely adherent to the urethral mucosa. It was freed gently from the mucosa with cup biopsy forceps, eased back into the bladder and removed. He made an uneventful recovery.

Comment

Superglue has been found as a foreign body in the external ear (Wright and Bull, 1987) but not as a foreign body in the urinary tract. In view of its renowned bonding strength our patient was fortunate that both fragments were removed so easily.

Acknowledgement

I thank Mr J. C. Smith, Consultant Urological Surgeon, Churchill Hospital, Oxford, for permission to report this case.

Reference

Wright, R. G. and Bull, P. D. (1987) Superglue ear. *J. Laryngol Otol.*, **101**, 706–707

Requests for reprints to W H. Turner, Department of Urology, Churchill Hospital, Headington, Oxford OX3 7LJ.

British Journal of Urology (1990), 66, 219–220
0007-1331/90/0066-0219/$10 00

Correspondence

Dear Sir,

re **Prostatectomy in the over 80-year-old.** M. G. Wyatt *et al. Br. J. Urol.*, **64**, 417–419, 1989.

In the above article, the cardiorespiratory status of the patients was graded according to the criteria described by Singh *et al.* (1973). A Grade 1 patient therefore has no significant concurrent disease, yet it is stated in the Results that of their 90 patients, 64 (71%) had severe concomitant cardiorespiratory disease of which 40 (44%) belonged to Grade 1. I am surely not alone in being unable to interpret these data.

While the authors are to be congratulated on their good results with prostatectomy in this age group, I do not consider that comparison with historical controls is valid. It would have been of much greater relevance to compare their results in this age group with the results of prostatectomy on their unit in younger patients over the same period of study. Perhaps then the value of some system of grading anaesthetic/operative risk, such as the A.S.A. grade, might have proved of value. The authors do not state how many patients were refused prostatectomy during this period, although they state that patient selection remains of considerable importance.

Yours sincerely,

J. C. Gingell
Department of Urology, Southmead General Hospital, Bristol.

Reply by M. G. Wyatt. The authors assure Mr Gingell that he is not alone in his difficulty in interpretation of the second paragraph of the Results section of our article. This should have read: "Severe concomitant disease coexisted in 64 patients (71%). Concomitant cardiorespiratory disease scored (Singh *et al.*, 1973) as follows: 40 (44%) Grade 1, 35 (39%) Grade 2 and 15 (17%) Grade 3."

The following Table provides further details. The first 3 categories, 50 patients in all, were either Grade 2 or 3. The remaining 40 patients were Grade 1.

Table Severe Concomitant Disease

1. Cardiorespiratory	38
2 Neuro (C V.A)	9
3. Diabetes	3
4 Rheumatoid arthritis	6
5. G I. malignancy	4
6. Myeloma	4
7 None	26
Total	90

With regard to the other points raised by Mr Gingell, no attempt was made to provide any control group and the authors have no information on patients refused prostatectomy during the period of this retrospective review.

We apologise for any confusion caused and hope that the point that age is no bar to prostatectomy has still been made.

Dear Sir,

re **Pharmacological management of erections during transurethral surgery.** T. A. McNicholas *et al. Br. J. Urol.*, **64**, 435–437, 1989.

I read with interest the above "Point of Technique" article. The authors highlight the importance of this particular problem, which is not so uncommon in day-to-day urological practice and about which little guidance is available in the literature.

I was involved with the management of a patient who developed full blown penile erection during cystoscopy and prior to the commencement of transurethral resection of prostate. Attempts at inducing detumescence by deepening the level of general anaesthesia and aspiration of blood from the corpora cavernosa were unsuccessful. The resection had to be abandoned after the patient had been under the anaesthetic for more than 45 minutes. The erection subsided after 3 hours. This experience prompted a survey of the literature which revealed a report by Sundien and Kolmert (*J. Urol.*, **138**, 411, 1987) on the use of intracorporeal ephedrine in such a situation. They described a series of 30 patients in whom 5 mg ephedrine were injected intracorporeally to relieve peri-operative erections. In all patients quick detumescence resulted with no post-operative complications.

I have had the opportunity of using intracorporeal ephedrine in 3 patients who developed penile erections during transurethral surgery; 5 mg of the drug were injected. It proved to be a very effective method to induce complete detumescence in approximately 3 minutes after the injection. There were no peri- or post-operative complications.

The advantage of ephedrine over phenylephrine and metaraminol is the easy availability of the drug in anaesthetic departments. Being an alpha and beta receptor stimulant, monitoring of systemic blood pressure is necessary.

Yours sincerely,

G. R. Mufti
Department of Urology, Walsgrave Hospital, Coventry.

Reply by Mr T. A. McNicholas. I would like to thank Mr Mufti for bringing this reference to my attention; his literature search was obviously more successful than ours. We would agree with the point of that reference and of his letter that ephedrine may well be a suitable agent. Ephedrine is more generally available and for that reason may be advantageous. We will assess it ourselves in due course. However, all urologists (and particularly those dealing with pharmacologically induced erections and their complications) should have a range of such drugs available, the monitoring equipment to observe blood pressure changes and hypotensive agents to deal with the hypertensive effects that may result from their use.

British Journal of Urology (1990), **66**, 221

Notices

British Association of Urological Surgeons

President: R. E. Williams, MD, ChM, FRCS, FRCSE

Annual Meeting: Glasgow. 25–28 June 1991

Abstracts of contributions to be considered as either papers, posters or videos by the Programme Sub-Committee of Council should be submitted on the special forms available from the BAUS Secretariat. Completed forms, which should state clearly whether the submission is a paper, a poster or a video, must be returned to the Honorary Secretary by Friday, 4 January 1991.

Abstracts not on the special forms will NOT be considered.

All correspondence to: R. J. Morgan, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

C.-E. Alken Prize

An endowment fund has been established to further clinical work and research in the field of Urology by presenting an annual award of SwF 10,000 for outstanding scientific endeavours. The award will be for an unpublished work in the field of Urology. An award certificate will also be presented. The prize money may be divided among several contributors.

The papers may be written in either German or English and three copies must be submitted by 30 September 1990 to: Stiftungsrat C.-E. Alken-Stiftung, Advokaturbüro Dr F. Kellerhals, Bundesplatz 4, CH-3011 Bern, Switzerland.

Each submission must be affixed with a code word and must not bear the author's name. In addition, a sealed envelope labelled with the code word is to be included, containing on a separate sheet of paper the author's name and professional standing, together with the code word.

The adjudicators for the award will be the Board of Directors of the endowment fund and their decision will be final.

The Surgitek Prize

The Prize consists of a fully sponsored visit to the American Urological Association Annual Five-day Meeting, together with a tour of Surgitek's manufacturing facility in Racine, Wisconsin. It is open to trainees in urology and consultants who are within 5 years of first appointment. Entrants should submit a written paper, which may be on any subject, but must be unpublished, and must not have been submitted previously for the Surgitek Prize, or other prizes. The winning entry will be the one which is considered to be "The most significant contribution to urology".

Entries will be judged by three members of BAUS Council nominated at the October meeting of Council. Papers should be submitted in triplicate to the Honorary Secretary by 1 January each year.

British Journal of Urology (1990), 66, 222–224

Diary

1990

August 16–27	15th International Cancer Congress, Hamburg, FR Germany. Contact: Secretariat, Letzter Hasenpfad 61, D-6000 Frankfurt 70, Federal Republic of Germany.
August 22–24	Edinburgh Urological Festival. Contact; Urological Festival Secretary, Department of Surgery/Urology, Western General Hospital, Crewe Road, Edinburgh EH4 2XU.
August 29– September 2	8th World Congress on Endourology and ESWL. 6th Annual Research Symposium on ESWL. 5th Triennial Meeting of International Society of Urologic Endoscopy. Washington DC, USA. Contact: Arthur Smith, Dept. Urology, Long Island Jewish Medical Centre, 270–05 76th Avenue, New Hyde Park, New York 11042.
September 9–11	Biannual Conference of International Society for Dynamics of the Upper Urinary Tract. Stockholm, Sweden. Contact Anne-Charlotte Kinn, Department of Urology, St Görans Sjukhus, 112 81 Stockholm, Sweden.
September 9–11	International Uro-gynaecological Association Meeting, Uppsala, Sweden. Contact: Secretariat, Stockholm Convention Bureau, PO Box 6911, S-10239 Stockholm, Sweden.
September 9–12	Congresso Nazionale Della Societa Italiana Di Urologia, Ancona, Italy. Contact: OMNIA Meeting and Congressi s.r.l., Piazza San Bernardo 109, 00187, Roma. Tel: (06) 47 41 202–49 18 77.
September 12–15	20th Annual Meeting of the International Continence Society, Aarhus, Denmark. Contact Dr J. P. Norgaard, Institute of Clinical Experimental Research, University of Aarhus, DK–8000 Aarhus C, Denmark. Tel: 45 86 12 55 55 ext. 3364.
September 27–28	Fifth Annual Paediatric Urology Course, Cambridge. Places are limited and early application is advisable. Contact Mr R. H. Whitaker, Department of Urology, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ.
September 30– October 7	New York Section, American Urological Association Meeting, Budapest. Contact Eva Sloane, New York Section, American Urological Association, 2 East 103rd Street, New York, NY 10029, USA.
October 1–4	92nd Congress of French Urology. Paris. Contact Convergences, Eurochirurgie—A.F.C. 90, 120 Avenue Gambetta, 75020 Paris, France.
October 4–5	Urological Management of Spinal Injury. Institute of Urology, London. Contact Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 01 240 9115.
October 5–6	BAUS Autumn Meeting, City Hospital, Nottingham. Contact BAUS office.
October 11	Female Incontinence Update, Derby City Hospital. Contact: Mr C. P. Chilton, Derby City Hospital, Uttoxeter Road, Derby DE3 3NE.

October 16–19	25th Annual Meeting of the Egyptian Urological Association. Cairo, Egypt. Contact Dr Ahmad S. Bedair, 26 Adly Street, Flat 908, Cairo, Egypt.
October 17–19	Advanced Stone Management Course. Institute of Urology, London. Contact Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 01 240 9115.
October 17–19	25th Annual Meeting of the Egyptian Urological Association, Cairo. Contact: The Congress Secretary Ahmad Samy Bedair MD, 26 Adly Street, Flat 908, Cairo, Egypt.
October 25–26	Urological Management of Spinal Injury, Institute of Urology, London. Contact: Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115.
October 25–29	Second International Congress on "The Pelvic Floor"—Update Management. Fort de France, Martinique. Contact Bureau Congress: I.F.R.U.G. "The Pelvic Floor", 2 Square La Fontaine, 2, Paris 75016, France.
November 8–9	Renal Failure and Transplantation. Guy's Hospital, London. Contact Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 01 240 9115.
November 10	Basic Science and Urology Symposium, Glasgow. Contact Mr R Scott, Department of Urology, Royal Infirmary, 16 Alexandra Parade, Glasgow G31 2ER.
1991	
January 4	Final date for submission of abstracts for 1991 BAUS Annual Meeting.
January 22–25	Eighth Copenhagen Symposium on Endoscopic Urological Surgery. Herlev Hospital, Herlev, Denmark. Contact F. Rasmussen, Department of Urology, Herlev Hospital, 2730 Herlev, Denmark.
February 3–6	International Conference on Orgasm. New Delhi, India. Contact Professor Prakash Kothari, First International Conference on Orgasm, 203 A, Sukhsagar. N. S. Patkar Marg, Bombay 400 007, India.
February 23–March 2	Royal Society of Medicine, Section of Urology, Vail, Colorado. Contact: M. H. Ashken, Consulting Rooms, BUPA Hospital, Old Watton Road, Colney, Norwich NR4 7SZ.
June 2–6	American Urological Association, Metro Toronto Convention Centre, Toronto, Canada.
June 16–20	Canadian Urological Association Annual Meeting, Ottowa. Contact: Dr R. B. Auld, Suite 620, 5991 Spring Garden Road, Halifax, Nova Scotia, Canada B3H 1Y6.
June 25–28	BAUS Annual Meeting, Scottish Exhibition and Conference Centre, Glasgow. Contact: BAUS office.
September 1–6	6th World Congress in Ultrasound, Copenhagen. Contact: Spadile Congress Service, Sommervej 3, DK-3100 Hornbaek, Denmark. Tel: 45 2 20 24 96.

September 4–7	Twenty-first Congress of the International Continence Society. Budapest, Hungary. Contact A. Tankó, Üllői ut 78/b, Department of Urology, Semmelweis Medical School, H-1082 Budapest, Hungary. Tel: (36) 1 1139 016.

1992

January 10	Final date for submission of abstracts for the 1992 BAUS Annual Meeting.
May 10–14	American Urological Association, Washington Convention Centre, Grand Hyatt, Washington DC.
June 21–26	BAUS Annual Meeting, Bournemouth International Centre, Bournemouth. Contact: BAUS Office.
June 22–25	Canadian Urological Association Annual Meeting, Winnipeg. Contact: Dr R. B. Auld, Suite 620, 5991 Spring Garden Road, Halifax, Nova Scotia, Canada B3H 1Y6.
August 24–27	Third European Symposium on Uroradiology. Herlev, Denmark. Contact Dr H. S. Thomsen, Department of Diagnostic Radiology 54E2, Herlev Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark.

1993

May 16–20	American Urological Association, San Antonio Convention Centre, San Antonio, Texas.
June 13–17	Canadian Urological Association Annual Meeting, Toronto. Contact: Dr R. B. Auld, Suite 620, 5991 Spring, Garden Road, Halifax, Nova Scotia, Canada B3H 1Y6.

1994

May 15–19	American Urological Association, Moscone Centre, San Francisco, California.

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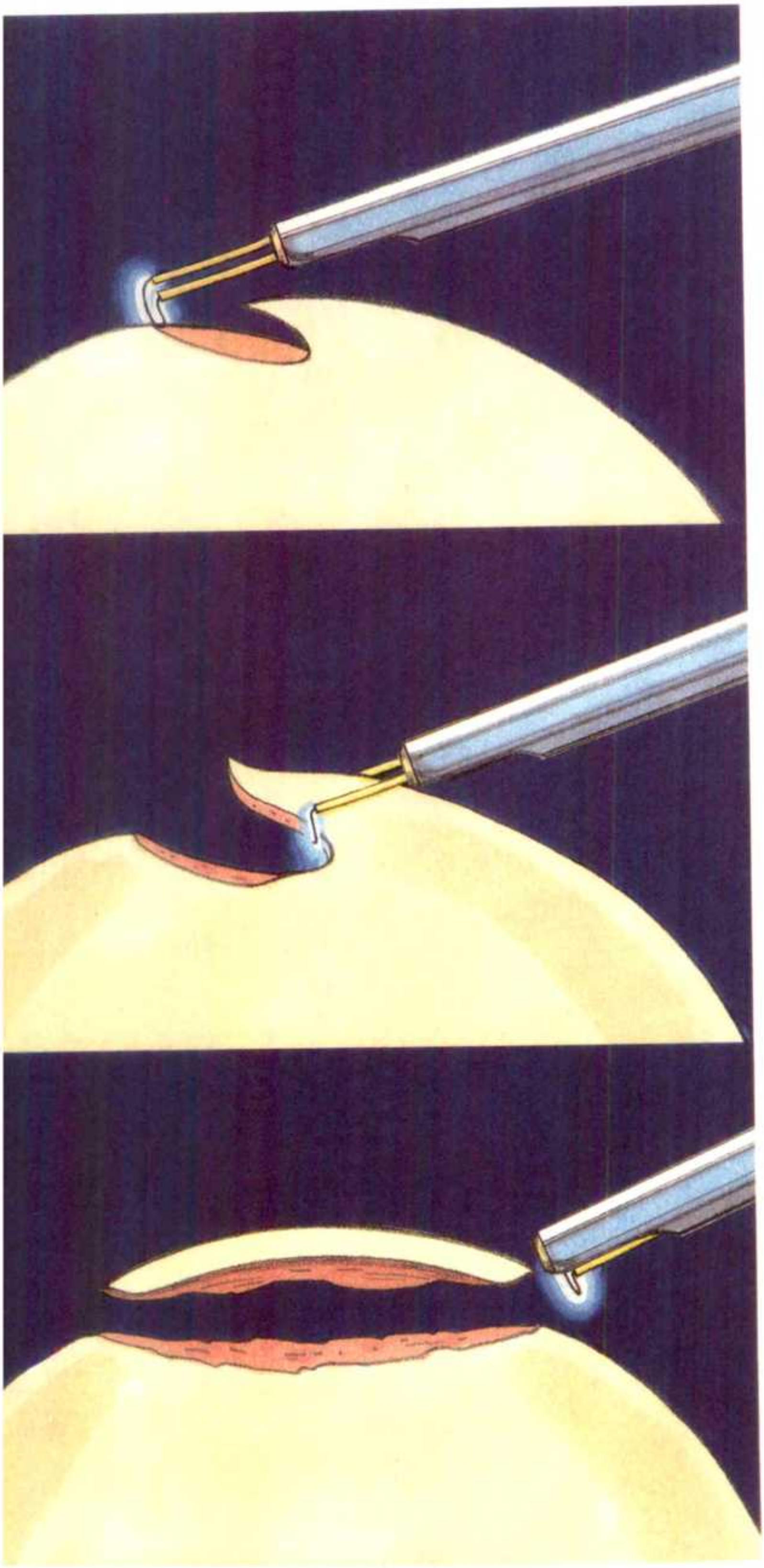

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REVIEW

Fetal Uropathy

D. F. M. THOMAS

Department of Paediatric Surgery, St James's University Hospital and General Infirmary, Leeds

Paediatric urology has been revolutionised by the advent of prenatal ultrasound diagnosis. Congenital urinary tract anomalies which previously presented with symptoms or complications in childhood are now being detected before birth on an ever increasing scale. Paediatric urologists in Western Europe and North America can realistically anticipate that within a decade virtually every child with a significant congenital uropathy will be identified *in utero*. Fetal surgery, the logical extension of prenatal diagnosis, has already been employed for the treatment of uropathy in a number of centres throughout the world. At first sight, therefore, prenatal urological diagnosis would appear to exemplify the benefits of sophisticated technology applied to the practice of clinical medicine. This may indeed be an accurate assessment of the impact of prenatal ultrasound on diagnosis and presentation, but its contribution to practical patient management is less certain.

Modern ultrasound has the capacity to yield a wealth of detailed anatomical information relating to the fetal urinary tract. Paediatric urologists are now in the position of having to learn how best to interpret and apply this information for the benefit of their patients. Very little is known about the natural history of some of the uropathies now being detected prenatally in infants who prove to be healthy and totally asymptomatic following delivery. As many as four-fifths of neonates with prenatally diagnosed uropathies have neither signs nor symptoms at birth (Thomas and Gordon, 1989). In these infants the urinary tract dilatation and any underlying urological disorder would have remained undetected had it not been for ultrasound imaging in pregnancy. It is doubtful whether we can simply apply to these asymptomatic infants the same therapeutic approaches and indications for surgical intervention that have been derived from previous experience of older children presenting with clinical disease. Prenatal diagnosis is an undoubted advance, but its incorporation into everyday clinical practice will require careful and critical appraisal.

Renal development—normal and abnormal

The fetal kidney has its origin in the metanephros—the most caudal of 3 blocks of mesoderm (the other 2 being the pronephros—a rudimentary non-functional kidney which undergoes complete regression—and the mesonephros). Differentiation of the primitive kidney is stimulated by the penetration of the metanephros by the ureteric bud, an outgrowth of the mesonephric duct during the fifth week of gestation. Division of the ureteric bud within the metanephros induces the development of primitive nephrons. The ureteric bud itself gives rise to the intrarenal collecting tubules in addition to the calices, renal pelvis and ureter. Branching of the intrarenal component is virtually complete by the fifteenth week of gestation and thus precedes the most active period of nephrogenesis—which occurs between 20 and 36 weeks (McCrory, 1972). Nephrogenesis ceases at around 36 weeks and thereafter the number of nephrons (approximately 1 million in a normal kidney) is fixed for life.

Fetal urine production occurs from around the eighth week of gestation. At this stage and throughout pregnancy the major physiological role of the fetal kidney is to contribute urine to the amniotic liquor. The presence of amniotic fluid in adequate volume is an essential factor in fetal lung development. Oligohydramnios is associated with pulmonary hypoplasia and compression deformities which are thought to occur because the developing fetus is deprived of the physical support of its normal fluid environment. In fetal life the essential excretory and homeostatic functions of the kidney are undertaken by the placenta. Fetal

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Accepted for publication 3 April 1990

and maternal plasma concentrations of creatinine, urea and electrolytes are identical. Even the fetus with bilateral renal agenesis, effectively dialysed by the placenta, can survive until delivery—at which stage it will probably die of pulmonary insufficiency before the effects of renal failure supervene.

In the last trimester of pregnancy large volumes of relatively dilute urine are produced. The amniotic fluid reaches its maximal volume of around 1000 ml at 38 weeks and its osmolality is generally below 250 mosmol/l. Using ultrasound to measure the volume of the fetal bladder and to observe the frequency of emptying, Nicolaides (unpublished data) estimated that the normal term fetus produces up to 40 ml of urine per hour. Immediately after birth the normal urine output drops to around 10 ml/h or less. It is possible that the high urine flow rate through the upper urinary tract during the last trimester may constitute a form of diuretic stress (flow uropathy) which might explain the relatively common finding of mild upper tract dilatation reverting to normal within the first year of post-natal life.

Our understanding of the embryology of renal anomalies and the pathophysiology of fetal uropathy is based partly on clinical studies and partly on the published findings of experimental work—particularly in the fetal lamb model. Beck (1971) reported experiments in which fetal lambs were operated upon to produce upper urinary tract obstruction by ligation of the ureter. Ligation performed during the first half of gestation resulted in the morphological and some of the histological characteristics of renal dysplasia. The same obstructive insult applied in the second half of the pregnancy gave rise to hydronephrosis in an otherwise recognisable kidney. Glick *et al.* (1983) also produced some, but not all, of the histological features of renal dysplasia in fetal lamb kidneys by ureteric occlusion in the first trimester. The importance of obstruction as a cause of dysplasia is supported by the clinical observation that the majority of multicystic dysplastic kidneys are associated with an atretic segment of the upper ureter or renal pelvis.

The pathophysiology of fetal obstructive uropathy has been comprehensively studied in San Francisco by Harrison *et al.* (1982a and b, 1983). Operating on third trimester fetal lambs, these authors developed a reliable technique for producing partial or complete urethral occlusion. The high pressure obstruction thus produced gave rise to severe hydronephrosis which was accompanied by pulmonary hypoplasia. Having established the animal model, Harrison's group then went on to demonstrate that intrauterine decompression by suprapubic cystostomy could reverse the renal changes and permit pulmonary maturation to continue. These experimental studies formed the basis for the San Francisco programme of human fetal surgery. Unfortunately the published experience of fetal surgery in man suggests that with rare exceptions, the lethal effects of obstructive uropathy, *i.e.* renal dysplasia and pulmonary hypoplasia, are irreversible by the time the uropathy is first detectable on ultrasound in the second trimester.

Urinary tract obstruction is not the only cause of renal dysplasia. An inherent abnormality of the metanephric blastema might also give rise to dysplasia. Another possible mechanism has been suggested by Mackie and Stephens (1975), who emphasised the crucial role of the ureteric bud in early renal development. They postulated that a ureteric bud arising from an abnormal or ectopic site on the mesonephric duct would be more likely to fuse with the peripheral zone of the metanephros—giving rise to dysplasia. In contrast, the normal ureteric bud penetrates the healthy central area of the metanephros. This attractive hypothesis is supported by clinical observations in duplex systems in which the upper pole parenchyma drained by an ectopic ureter is usually dysplastic. The ureteric bud hypothesis has also been invoked to explain reflux nephropathy, *i.e.* the lateral position of the refluxing ureteric orifice is regarded as evidence of ureteric ectopia and the renal damage which is found in 30 to 50% of children with reflux is viewed as evidence of associated renal dysplasia. In this context the ureteric bud hypothesis is, perhaps, less convincing. Until recently the majority of children with reflux were identified only after they had presented with infection. In this situation it is usually difficult to determine whether the associated renal damage is congenital (dysplasia) or acquired (post-infective in origin).

Prenatal diagnosis offers an exciting opportunity to increase our understanding of the aetiology and the natural history of many renal anomalies. Unfortunately the potential for preventing renal dysplasia appears to be very limited. The only mechanism that might be amenable to intrauterine intervention is that of obstructive uropathy—for which the results of intrauterine intervention have so far been disappointing.

Diagnostic accuracy

Kramer (1983), writing from the Mayo Clinic, stated that "ultrasonography may identify accurately up to 90% of fetal kidneys by 17 to 20 weeks of gestation and 95% by 22 weeks of gestation". The pace of technological advance is such that virtually every district obstetric unit in the United Kingdom is now equipped to match this level of accuracy. Specialist centres would now aim to identify almost 100% of normal fetal kidneys at 17 to 19 weeks (the usual timing of a "routine" dating scan), whilst severely dilated systems are not uncommonly identified as early as 12 to 14 weeks. State of the art ultrasound is impressive technology, but we must not lose sight of its limitations. Ultrasound provides detailed anatomical information, usually relating to dilatation, and nothing more. It cannot, for example, distinguish between ureteric dilatation due to obstruction at the vesicoureteric junction and dilatation related to vesicoureteric reflux. This distinction can only be made reliably by the use of voiding cystography in postnatal life (intrauterine cystography is technically feasible but rarely justifiable). Nor does ultrasound reliably distinguish between high pressure obstructive dilatation (*e.g.* associated with urethral obstruction) and low pressure non-obstructive dilatation (*e.g.* prune belly syndrome or primary reflux). Ultrasound tells us nothing about renal function. This is perhaps an over-critical assessment, since in the hands of an experienced radiologist certain additional clues can often by deduced from ultrasound. For example, ureteric dilatation which shows marked variation in degree is more likely to be due to reflux than to obstruction—which is generally associated with a fixed degree of dilatation. A marked reduction in the amniotic liquor volume is often an indicator of poor urinary output and gross renal impairment. Further evidence of poor function and dysplasia can be inferred from ultrasound appearances of "bright" echogenic renal parenchyma. However, these ultrasound appearances are at best clues rather than reliable prognostic indicators. For the purposes of routine clinical practice it is safer to regard prenatal ultrasound imaging as a screening tool which serves 2 important roles:

1. The detection of severely affected fetuses at a stage in gestation when termination of pregnancy is still a feasible and legal option.
2. The identification of significant degrees of urinary tract dilatation which merit investigation in early postnatal life.

The "accuracy" of prenatal diagnosis has been interpreted in various ways by different authors. Some early studies reported impressively high levels of diagnostic "accuracy": for example, the figures of 89% quoted by Hutson *et al.* (1985), 86% (Pocock *et al.*, 1985) and 77% (Grignon *et al.*, 1986). In contrast, Clarke *et al.* (1989) reported a series from Manchester in which the correct prenatal diagnosis was reached in only 28 of 91 cases, a diagnostic "accuracy" rate of 31%. There is a simple explanation for these discrepancies. Clarke and his coauthors chose to define "accuracy" as the ability of prenatal imaging to predict the final urological diagnosis. In contrast, the authors of most other studies have adopted less stringent definitions and have generally confined themselves to the capacity of ultrasound to detect dilatation or "hydronephrosis".

Two additional factors have a major influence on diagnostic accuracy:

1. The definition of "significant" or "pathological" dilatation. Modern ultrasound can demonstrate minor degrees of dilatation and although attempts have been made to define the upper limit of normality of the fetal collecting systems, there is little general agreement as to what represents a pathological degree of dilatation. Many mildly dilated systems are probably within the upper limits of normality and it is potentially misleading to regard them as uropathies for the purposes of publication.

2. Timing of routine ultrasound scanning in pregnancy. Most uropathies are undetectable until they give rise to dilatation. If scanning is limited to a single examination early in pregnancy, between 17 and 19 weeks, severe anomalies suitable for termination will be detected, but the majority of non-lethal uropathies will be missed. In a prospective study by Helin and Persson (1986) 11,986 pregnancies were scanned at 17 and 33 weeks; 33 urological abnormalities were identified, only 3 of which (9%) were detected on the 17-week scan. The remaining 30 uropathies were not evident until the second scan at 33 weeks. The pick-up rate of prenatal diagnosis is therefore dependent to a large extent upon the gestational age at which ultrasound scans are routinely performed.

Incidence of fetal uropathy

Calculations of the incidence of fetal uropathy are influenced by the same factors which affect any consideration of diagnostic accuracy. These include the problem of defining pathological as opposed to physiological degrees of dilatation and the varying detection rate of ultrasound at different stages in pregnancy. A study based on scanning in late pregnancy will report a higher incidence of fetal uropathy than one based on scans undertaken at a lower mean gestational age. In the study by Livera *et al.* (1989), pregnancies were scanned at 28 weeks; 92 abnormal renal scans were identified in a total of 6292 pregnancies. In only 42 of these cases, however, was the presence of a significant urological anomaly confirmed following delivery; 47 infants (52%) were found on postnatal imaging to have either a normal urinary tract or a normal extrarenal pelvis. In this study, therefore, more than half of the prenatal diagnoses of uropathy must be regarded as false positive findings. The false negative rate, *i.e. significant* urological abnormalities missed by ultrasound at 28 weeks, was low. Only 7 unsuspected uropathies (5 of which were reflux) became clinically apparent during the 18-month period of follow-up. Scott and Renwick (1988) reported a 22% "false positive" rate in their comprehensive study of prenatally diagnosed congenital abnormalities in the Northern Region.

Estimates of the incidence of fetal uropathy derived from some of the more recently published studies are summarised in Table 1. Current evidence suggests that the overall incidence of detectable dilatation is of the order of 1 in 100 pregnancies, whereas the incidence of significant uropathy, for which postnatal intervention or termination of pregnancy is appropriate, is of the order of 1 in 500 pregnancies. The eventual pick-up rate of significant uropathies is likely to be comparable to the incidence of renal abnormalities reported from large post mortem studies, for example an analysis of 245,000 autopsies which yielded an incidence of renal abnormalities of 1 in 650 (Ashley and Mostofi, 1960).

Anatomical classification of fetal uropathy

The more common causes of fetal uropathy are listed in Table 2. Lethal forms of urethral obstruction are more often due to urethral atresia or hypoplasia rather than the clearly defined membrane or cusps of classical posterior urethral valves.

Table 1 Incidence of Fetal Uropathy

Incidence	*Centre*	*Authors*
1.1200	Lund	Kullendorf *et al* (1984)
1:935	Derby	Watson *et al* (1988)
1:600	Leeds	Arthur *et al.* (1989)
1·330	Malmo	Helin and Persson (1986)
1.154	Stoke	Livera *et al.* (1989)

Table 2 Types of Fetal Uropathy

Bilateral	*Unilateral*
Urethral obstruction, *e.g.* posterior urethral valves, urethral atresia	Pelviureteric obstruction Multicystic kidney Vesicoureteric reflux
Bilateral upper tract pathology, *e.g.* pelviureteric junction obstruction, vesicoureter reflux, *etc*	Vesicoureteric junction obstruction Renal duplication, *e.g.* obstructed upper pole
Non-obstructive dilatation, *e.g.* prune belly syndrome	Renal agenesis, polycystic disease, *etc*

Although prune belly syndrome is described as a low pressure, non-obstructive form of dilatation, it is possible that obstruction does exist *in utero*, but resolves spontaneously to leave persisting dilatation of the bladder and upper tracts.

Upper tract pathology such as pelviureteric obstruction may be unilateral or bilateral in distribution. Bilateral multicystic dysplasia is a lethal anomaly. Pelviureteric obstruction is the most frequent significant non-lethal uropathy, accounting for approximately 50% of cases. Vesicoureteric reflux and multicystic dysplasia each contribute about 15% to the total, whilst posterior urethral valve obstruction accounts for around 10% of significant uropathies in live-born neonates. The remaining 10% consists of a variety of less common conditions, *e.g.* renal agenesis, upper tract duplication, crossed ectopia, *etc.*

Management of fetal uropathy

Intrauterine intervention is appropriate only in severe cases of bilateral uropathy. There can be no ethical justification for attempting to drain a unilateral hydronephrosis *in utero*. Intrauterine intervention can take 1 of 3 forms: termination of pregnancy, intrauterine drainage (fetal surgery), or elective induction of pre-term labour.

Termination of pregnancy. This is undoubtedly the most widely practised form of intervention. The decision to offer termination may be reinforced by the discovery of coexistent abnormalities—which are relatively common in fetuses with bilateral uropathy. Arthur *et al.* (1989) identified serious coexistent abnormalities or syndromes in 26% of fetuses with bilateral uropathies. In contrast, only 3% of those with unilateral uropathy had severe coexistent pathology. The decision to offer termination will be based on a combination of factors, such as karyotype, oligohydramnios, "bright" dysplastic renal cortex and evidence of gross bilateral uropathy or severe bladder outflow obstruction. The prognosis can be refined by biochemical analysis of fetal urine (obtained by percutaneous bladder puncture). Estimation of the fetal urinary sodium and osmolality (Glick *et al.*, 1985) are the most widely used prognostic indicators, but others are being actively developed (Nicolaides, unpublished data).

Intrauterine intervention (fetal surgery). In the first reported case (Harrison *et al.*, 1982b), a 21-week-gestation fetus with urethral valves was delivered via hysterotomy and underwent bilateral cutaneous ureterostomies. The fetus was then returned to the uterus and subsequently delivered at 35 weeks. Although adequate upper tract drainage had been obtained, the infant nevertheless succumbed to pulmonary hypoplasia within the first few hours of life. This disappointing outcome did not diminish enthusiasm for the concept. Obstetricians throughout the world have subsequently undertaken intrauterine drainage, largely on an uncontrolled and unreported basis. The favoured technique has consisted of the percutaneous insertion of a pigtail suprapubic catheter (vesico-amniotic shunt) to drain fetal urine from the obstructed bladder into the amniotic fluid. Initial data from a number of centres were published in 1986 in the format of a report by the International Fetal Surgery Registry (Manning *et al.*, 1986). Of the 73 fetuses treated *in utero*, 27 (37%) nevertheless succumbed to pulmonary hypoplasia in the neonatal period. In a further 11 cases the pregnancy was subsequently terminated. It is likely that these would also have resulted in neonatal death if they had run to term. The Fetal Surgery Registry reported an overall mortality rate of 59%. In addition to these cases, a further 57 have been identified in the English literature in a review undertaken by Elder *et al.* (1987). The outcome was hardly encouraging: 33 (45%) of the 57 reported cases were associated with complications such as migration or malfunction of the shunt (19%), onset of premature labour (12%), urinary ascites (7%), *etc.* Elder's review identified 28 fetuses with associated oligohydramnios—of whom only 6 (21%) survived.

The San Francisco group (Crumbleholme *et al.*, 1988) have persisted with hysterotomy and open fetal surgery in the belief that it provides more reliable upper tract decompression. They have reported their experience of open fetal surgical procedures in 5 fetuses selected from over 200 referred for possible intervention. Despite surgery, 2 neonates died from pulmonary hypoplasia and a third died of unrelated causes. Of the 2 survivors, 1 is now in renal failure and only 1 has normal renal function.

The current status of fetal surgery is as an experimental technique which should now be confined to a handful of centres. There is no evidence to support its routine use in normal clinical practice. The available evidence suggests that in the overwhelming majority of affected fetuses, the lethal pulmonary and renal damage is already irreversible by the time the underlying uropathy can first be detected on ultrasound. Non-lethal uropathies are best managed by appropriate investigation and prompt treatment in early postnatal life.

Elective premature delivery. Benefits are purely theoretical and would have to be offset against the undoubted risks of premature birth. It is likely that the majority of obstructed systems have already reached a functional equilibrium by the time that induction of premature labour could be safely contemplated at 35 to 36 weeks.

Postnatal management

It is hoped that the advent of prenatal diagnosis will be reflected in an ultimate reduction in the number of individuals with congenital uropathies on end-stage renal failure programmes. However, it is important not to overstate the probable benefits. A recent analysis of 258 live born infants (Thomas and Crabbe, unpublished data) identified only 44 neonates (17%) in whom the prenatal diagnosis has been of definite value in revealing a clinically undetectable uropathy which presented a significant potential threat to renal function (involving both upper tracts or a solitary kidney).

A simplified scheme for postnatal investigation is outlined in Figure 1. Centres differ in the timing of various investigations and their use of cystography. Neonates are relatively underhydrated in the first 24 h of life and for this reason the initial ultrasound scan is best deferred until around 24 to 48 h of age, when the urinary tract is subjected to a more representative fluid load. Ultrasound findings of ureteric or bladder dilatation justify an early micturating cystourethrogram, (MCU) but this investigation can reasonably be omitted if an experienced radiologist is confident that the dilatation is confined to the pelvis and calices, *i.e.* presumed pelviureteric junction obstruction. Functional imaging, particularly intravenous urography, is often unrewarding in the first few weeks of life. Even isotope imaging can be unreliable during the

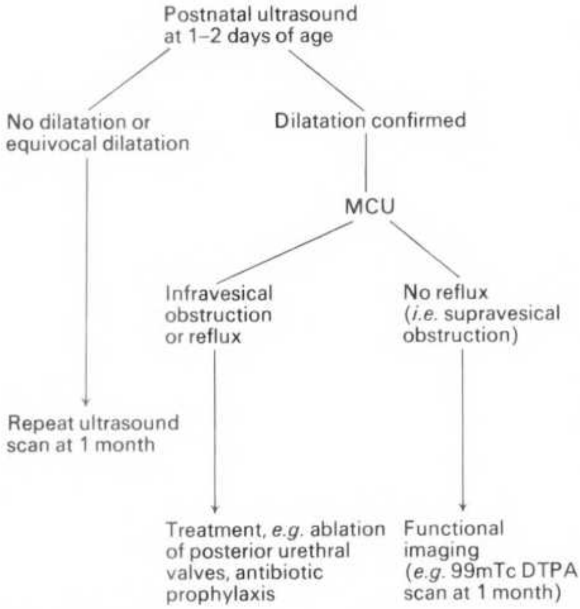
Postnatal ultrasound at 1–2 days of age
No dilatation or equivocal dilatation
Dilatation confirmed
MCU
Infravesical obstruction or reflux
No reflux (*i.e.* supravesical obstruction)
Repeat ultrasound scan at 1 month
Treatment, *e.g.* ablation of posterior urethral valves, antibiotic prophylaxis
Functional imaging (*e.g.* 99mTc DTPA scan at 1 month)

Fig. 1 Scheme for postnatal investigation.

period of "transitional nephrology" and where possible should be deferred until around 4 weeks of age. The aims of postnatal investigation and the limitations of various imaging modalities have recently been reviewed by Hanbury *et al.* (1989).

Detailed consideration of the postnatal management of fetal uropathies is beyond the scope of this review. The aims of management can be summarised as the need to safeguard renal function and prevent urinary infection whilst recognising that the natural history of untreated fetal uropathies is in many instances not known (Fig. 2). The management of prenatally diagnosed pelviureteric junction obstruction (the most common prenatally diagnosed uropathy) is the subject of considerable controversy. Multicystic dysplastic kidney has been revealed by prenatal diagnosis to be a more common lesion than was previously recognised. Is there still a case for routine nephrectomy or can asymptomatic multicystic dysplastic kidneys be safely left *in situ*? Major grades of vesicoureteric reflux can now be detected *in utero*. Should we apply to these asymptomatic infants (predominantly male) the same regimen of investigation, antibiotic prophylaxis and regular urine analysis as we apply to children whose reflux has presented with infection? In what proportion of infants with mildly dilated systems is reflux the underlying cause? The prenatal detection of posterior urethral valve obstruction would appear to be beneficial, but long-term studies will be required to determine whether there is a genuine reduction in the proportion of boys destined for renal failure at puberty. Other questions relate to the ethics and logistics of prenatal diagnosis. Should

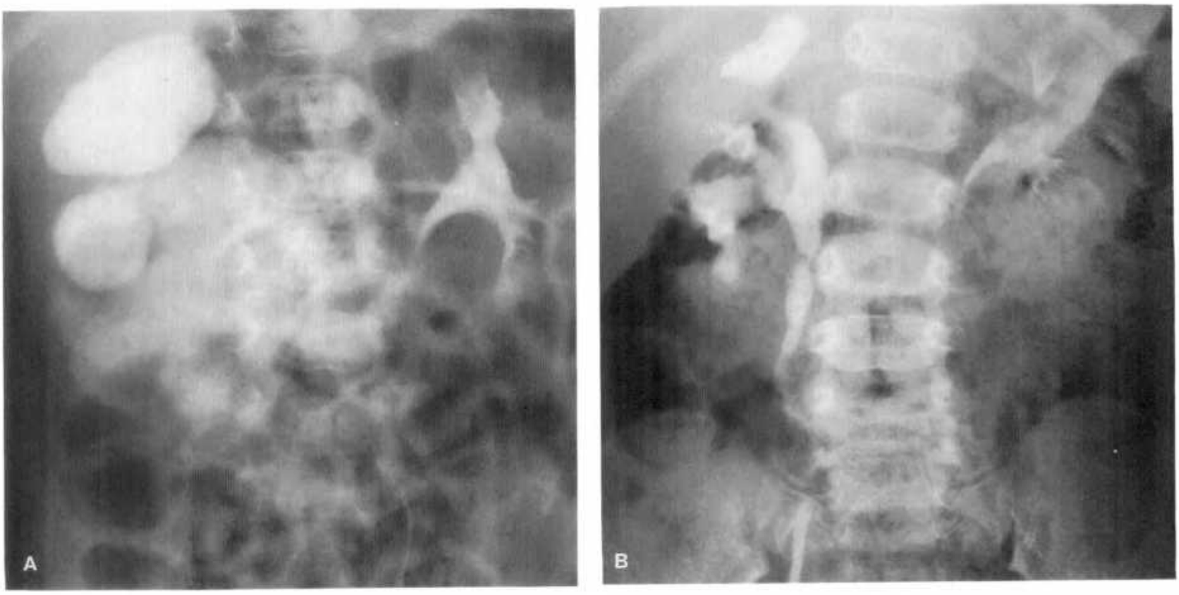

Fig. 2 (A) Intravenous urogram at 1 month demonstrating prenatally diagnosed right pelviureteric obstruction which was confirmed by isotope renography. Conservative management. (B) Follow-up IVU in same infant at 15 months. Resolution of hydronephrosis without pyeloplasty. How many infants with prenatally diagnosed pelviureteric obstruction currently undergo unnecessary early pyeloplasty? How many self-limiting obstructions will recur in later life?

parents be informed of ultrasound findings which are unlikely to influence the management of the pregnancy but will probably generate considerable anxiety?

The question of logistics is easier to resolve. The ideal arrangement is probably shared care undertaken on the one hand by a regional team consisting of a paediatric urologist, nephrologist and radiologist and on the other by the child's district paediatrician who can oversee follow-up and urine analysis on a regular basis. Prenatal diagnosis is here to stay and will be the major factor determining the development of paediatric urology for the next decade.

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The Author

D F. M Thomas, MRCP, FRCS, Consultant Paediatric Urologist/Surgeon, St James's University Hospital, Leeds LS9 7TF.

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Nuclear Techniques for the Analysis of Urinary Calculi

A. SAINT and N. A. DYSON

School of Physics and Space Research, University of Birmingham, Birmingham

Summary—Sections of urinary calculi were prepared and point-by-point analyses along a line-scan were carried out using the techniques of proton-induced X-ray emission (PIXE) and nuclear reaction analysis (NRA). Correlations between several pairs of elements (including trace elements) were noted and it was also clear that the composition of a stone varied markedly at different stages of development.

Proton induced X-ray emission (PIXE) analysis has been used to quantify trace elements in a number of biological materials (Khan and Crumpton, 1981). This technique provides high sensitivity combined with simultaneous multi-element analysis. It also provides a non-destructive method of spatially analysing a sample to study lateral variations in element concentration.

To carry out the analyses reported in the present study several stones were sectioned, including a section through the nucleus (or nidus) of the stone, and a point-by-point analysis was performed across the centre of each section. Such an analysis provides information on point-to-point differences in composition, in particular between the nidus and the outer layers formed by subsequent deposition of material.

The method of proton-induced X-ray emission analysis was used by Taylor and Saied (1982), who reported the presence of several trace elements in the interior regions of an organic stone, and at the centre. The aim of the present study was to apply this technique, together with a nuclear analytical technique known as nuclear reaction analysis, or NRA (Amsel *et al.*, 1971), to investigate in some detail the concentrations and distribution of trace elements in urinary calculi.

Materials and Methods

The use of X-ray fluorescence analysis (XRF) has been advancing for many years. This technique involves the use of a primary X-ray source to generate characteristic X-rays in the sample. The development of high resolution silicon detectors has made this technique fast and efficient. One way of increasing the sensitivity of X-ray emission analysis is to use heavy energetic charged particles to excite the X-ray emission, as in the work reported here. This is known as particle-induced X-ray emission or PIXE analysis. Some of the reasons for this increased sensitivity will now be discussed.

The first charged particles to be used to produce characteristic X-rays were electrons. This principle has been applied to elemental analysis in the widely used electron microprobe. Electrons, however, produce relatively large amounts of background radiation ("Bremsstrahlung"), which limits the visibility of peaks produced by elements which are present in low concentration. It is a feature of proton bombardment that less background radiation is produced, leading to an increased ability to detect trace elements.

For a PIXE analysis to have a greater sensitivity than XRF or an electron-induced X-ray technique such as electron microanalysis, it must not only produce less background, but also produce comparable amounts of characteristic radiation. This can be investigated by looking at the ionization cross-section, for protons and electrons. A great deal of experimental and theoretical work has established that protons and electrons will produce comparable numbers of X-rays, provided their velocities are the same. This means that protons will require an energy of 2 to 4 MeV to produce the same characteristic X-ray count as the 10 to 100 keV

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electrons used in scanning electron microscopy and the electron microprobe. Protons of a few MeV energy are readily available from small nuclear accelerators such as the machine used in the present work.

A proton beam can also be collimated to a fine pencil to facilitate spatial analysis. PIXE is, therefore, an ideal tool with which to study the spatial variation of trace elements in urinary calculi.

If useful information on trace element concentrations is to be found from such an analysis, a method of identifying the bulk constituents of the stone is also needed. The mineral composition of the stone can easily be found from PIXE data, since the calcium, present in the mineral phase, gives readily detactable X-rays. The low energy X-rays produced by the low Z constituents (C, O, N) of the organic phase are, however, not easily detectable. This organic phase is therefore monitored using the γ-ray yield from the $^{15}N(p,\alpha\gamma)^{12}C$ nuclear reaction. In this reaction the naturally-occurring isotope ^{15}N yields, when bombarded by protons, an α-particle and a γ-ray photon. The latter may be detected and measured quantitatively and gives an index of the concentration of nitrogen present at that point in the sample. Nitrogen is used because it is present in the organic phase only, whereas carbon and oxygen may be present in the mineral phase as calcium oxalate or carbonate. This is an NRA technique known as proton-induced gamma-ray emission (PIGME) analysis.

Because the $^{15}N(p,\alpha\gamma)^{12}C$ reaction is induced with protons, this analysis can be carried out simultaneously with PIXE. The natural abundance of ^{15}N is only 0.4% but, due to the very large cross-section for this reaction, protein, uric acid and urea can be detected to about 0.1% in the stone sections.

All of the analyses were carried out using the Dynamitron accelerator in the Radiation Centre of the School of Physics and Space Research, Birmingham University.

Over the past few years a special beam line facility has been developed at the Radiation Centre to deal with all types of accelerator-based analysis. A schematic of the particular chamber used in this work is shown in Figure 1. This chamber was chosen because it allows the samples to be translated across the beam for spatial analysis. The chamber also allows the simultaneous use of a lithium drifted silicon X-ray detector and a sodium iodide γ-ray detector, with the data collection system allowing data from both detectors to be collected simultaneously.

A beam of 2.5 MeV protons was used for this work and was collimated to a diameter of 1 mm. The beam was then passed through a 1.5 mm "beam-scraper", which prevents any edge-scattered beam from entering the chamber. As can be seen from Figure 1, the target chamber is electrically isolated from the rest of the beam line. This allows the beam current to be monitored directly from the chamber. The total charge deposited for each analysis was 25 μC at a beam current in the region of 10 nA. The charge could be measured with an accuracy of 3%. The beam appeared to carbonise the samples to some degree, but consecutive data accumulation on the same spot showed that this had a negligible effect on the trace element concentrations.

The results were obtained as dual 2K multiplexed spectra, the first 1024 channels being a PIXE spectrum and the second 1024 channels being the PIGME spectrum. Specimen spectra are shown in Figure 2. A pair of these spectra is produced for each point in the scan.

Once the X-ray yield has been measured, the elemental concentration may be calculated from the standards, which are described below. This requires a knowledge of several parameters, particularly the cross-sections for X-ray production, the proton stopping-power for sample and standards, and the fluorescence yields for the several elements under investigation and for the standard.

A detailed account of these procedures has been given by several authors, particularly Folkmann *et al.* (1974) and Campbell and Cookson (1984), who discuss in detail the several steps necessary to obtain a quantitative result with the type of specimen and standard used in the present work.

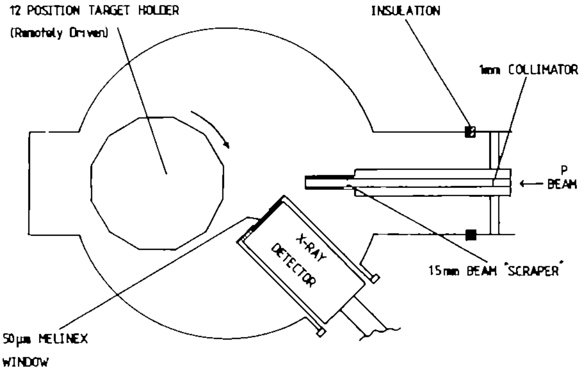

Fig. 1 Experimental arrangement showing the relative position of proton beam, target holder and X-ray detector. (The scintillation counter used for the nuclear reaction analysis was positioned perpendicular to the target chamber and close to the target.)

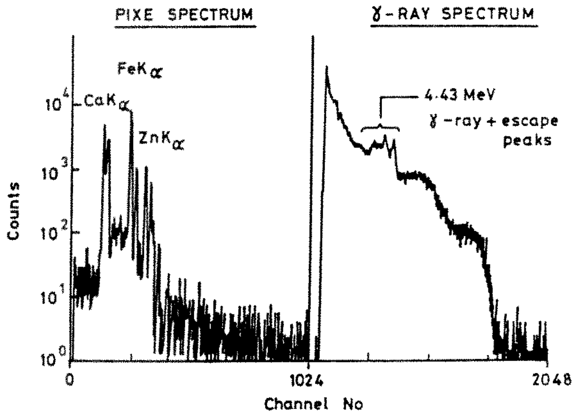

Fig. 2 Specimen spectra of X-rays (from the PIXE technique) and γ-rays (from the nuclear reaction analysis).

Sample Preparation

Samples of urinary calculi (all primary bladder stones) were obtained from 4 patients at the Dudley Road Hospital, Birmingham. The stones varied in size, colour and visual morphology. Both sectioned and homogeneous samples were prepared from the 4 stones and samples from each were subjected to chemical analysis.

The stones were sectioned using a macrotome. Each stone was first mounted in wax and the first cut passed as close to the visual centre of the stone as possible. Each half of the stone was then cut into sections 2 to 3 mm thick. Selected sections were mounted on aluminium foil for structural stability and then coated with a thin (a few tens of nm) carbon film to prevent beam charging effects in the proton beam. A small piece of the carbon rod used to coat the samples was also analysed, but no significant contamination with other elements was found.

Homogeneous samples were prepared by grinding small pieces of calculi to a fine powder in an agate ball mill. Agate was used for both the barrel and the ball to reduce metallic contamination. The powder produced was pressed in a hydraulic press—set at 3 tons—for 1 min to produce a pellet 1 cm in diameter and approximately 2 mm thick. The pellets had a coherence which was sufficient to render unnecessary the addition of any binding agent. These samples were also carbon coated, to avoid surface charging.

External standards were prepared and used to characterise these samples. The bulk composition of a section may vary widely across its surface, thus making uniform doping of such a sample difficult. The method of internal standards is, therefore, too difficult to implement.

The standards were prepared using a mixture of $CaSO_4$ and cellulose to produce a matrix of approximately 20% calcium by weight. This was the approximate composition of the ground calculi samples. Five portions of this matrix were doped with aliquots of standard solutions of arsenic, an element unlikely to be found in any of the materials used in the preparation of the standards. From the intensity of the arsenic X-rays emitted from these samples and the known cross-sections for X-ray production, the concentration of several elements in the stones could be determined.

Analysis of these standards produced a linear relationship between X-ray intensity and arsenic concentration, with a linear correlation coefficient of 0.995.

Two sets of standards were also prepared for the assay of organic nitrogen in the calculi. The first set consisted of a series of compounds of known nitrogen content—urea, asparagine, alanine and aspartic acid—from which pressed pellets were formed. The second set was prepared by mixing, in known ratios, small amounts of the 20% calcium matrix with well known amounts of urea.

In addition to PIXE and NRA analysis, qualitative chemical analysis was performed on each stone.

Results and Data Processing

The results of the analysis are presented here as graphs of beam position v. elemental concentration. These graphs are shown in Figures 3 to 6. It may be noted that if the absolute concentrations were not needed, it would be possible to omit the detailed computational procedure referred to above and simply present the counting rates observed in the appropriate X-ray peaks as a function of position.

The chemical analyses are summarised in Table 1.

To make the data more quantitative, tables of correlation coefficients were calculated for each scan. These results are given in Tables 2 to 5; correlations significant at $P=0.1$ and $P=0.05$, or 0.05 and 0.01, are specially indicated.

The four stones, designated A–D, will now be considered in turn.

Table 1 Chemical Test Results

Stone	*Most probable bulk constituents*
A	Mixed Ca oxalate/Uric acid stone with small amounts of Ca phosphate.
B	Mixed Ca oxalate/Ca phosphate stone containing some uric acid.
C	Mixed Ca oxalate/Ca phosphate stone.
D	Uric acid stone containing some Ca phosphate.

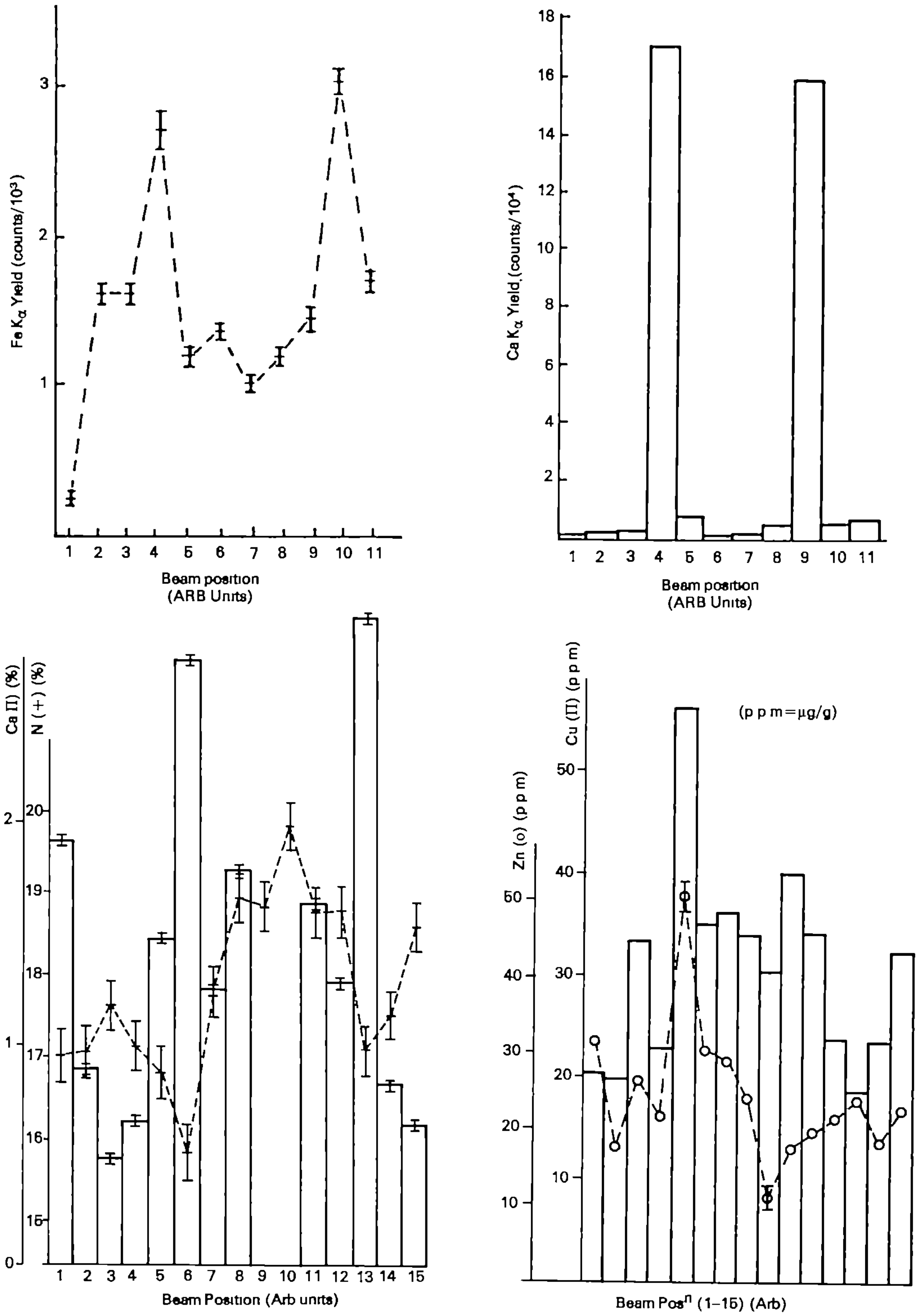

Fig. 3 (A) Distributions of calcium and iron across section A4, showing strong correlation (The measurements of calcium and iron were obtained from 2 different scans along the same line The "beam position" numbers do not therefore register exactly similarly in the 2 cases) (B) Distributions of calcium and nitrogen across section A2 (C) Distributions of zinc and copper across section A2

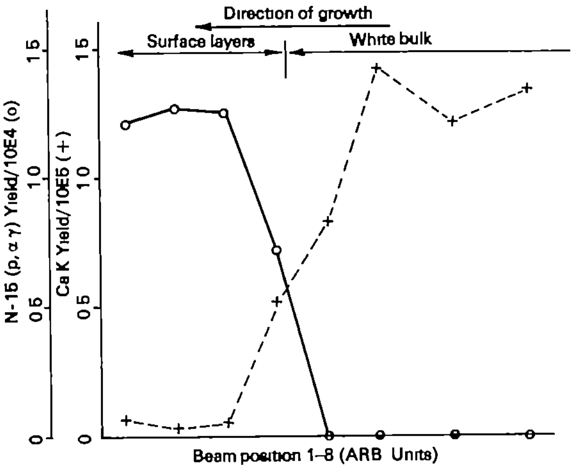

Fig. 4 Distributions of nitrogen and calcium across section B1.

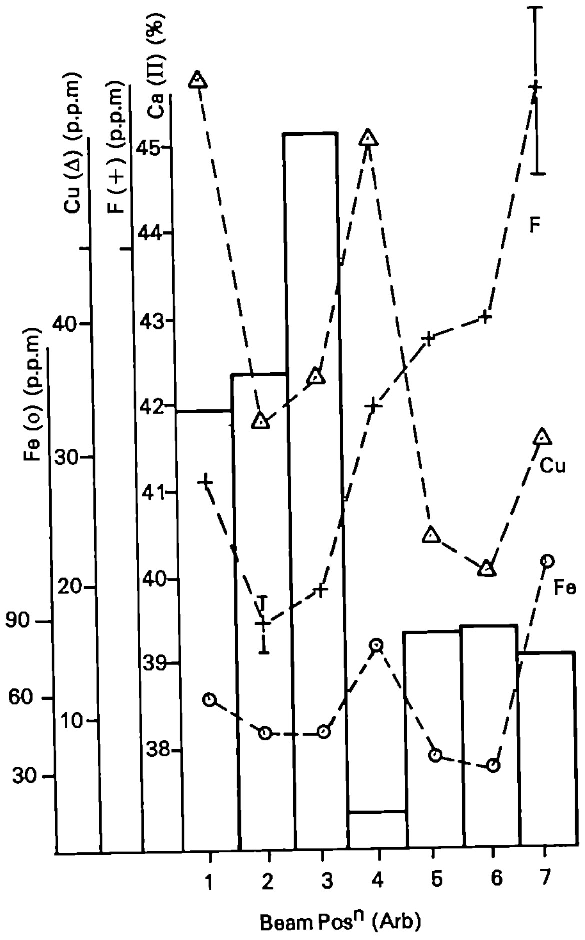

Fig. 5 Distributions of calcium, fluorine, copper and iron across section C1

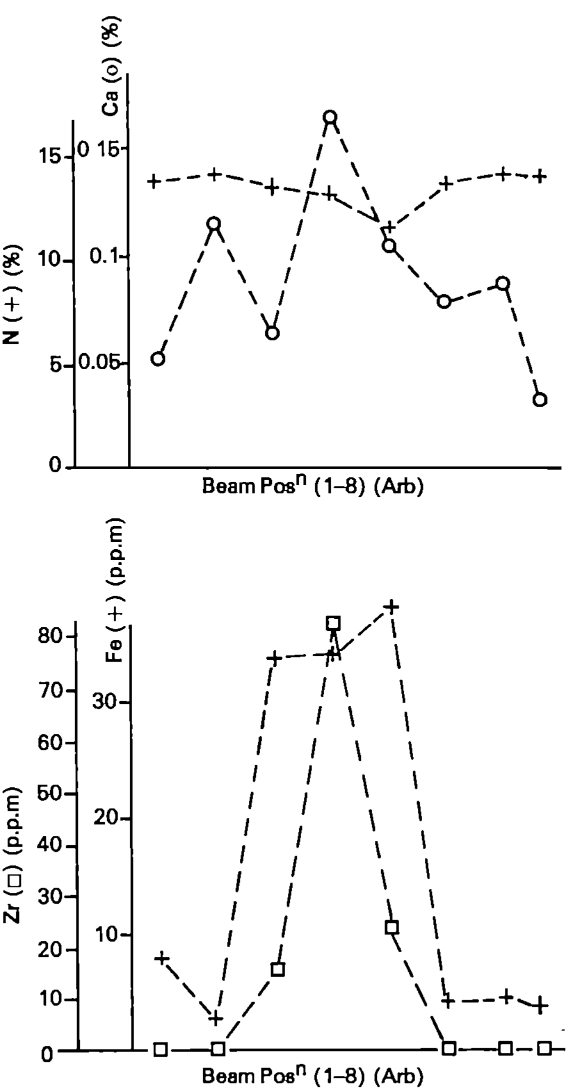

Fig. 6 Distributions of nitrogen, calcium, iron and zirconium across section D1.

Stone A. This was found to be a mixed calcium oxalate/uric acid stone with small amounts of calcium phosphate. Four sections were prepared (numbered A1–A4) and were analysed point-by-point using the PIXE and PIGME techniques outlined above. Only the most significant results are presented here. Some results are presented in Figures 3A, B and C. To interpret the role of trace elements in stone formation it is necessary to investigate the bulk constituents, so that the trace element distribution can be correlated to bulk compositional changes as the stone grows. This is well illustrated in Figure 3A, obtained with section

Table 2 Linear Correlation Coefficients—Section A2

Element	*1/N*	*Ca*	*Fe*	*Cu*	*Zn*	*Pb*	*Br*	*Sr*
1/N	1.0	0.563*	0.353	−0.093	0.453	0.168	−0.364	0.632*
Ca	—	1.0	−0.120	−0.126	0.365	0.577*	0.141	0.403
Fe	—	—	1.0	0.248	0.349	−0.121	−0.379	0.104
Cu	—	—	—	1.0	0.691†	−0.294	−0.357	−0.274
Zn	—	—	—	—	1.0	−0.111	−0.683†	0.095
Pb	—	—	—	—	—	1.0	0.257	0.309
Br	—	—	—	—	—	—	1.0	0.191

* Significant correlation at $P \simeq 0.05$
† Significant correlation at $P \simeq 0.01$

Table 3 Linear Correlation Coefficients—Section B1

Element	*Ca*	*Fe*	*Cu*	*Zn*	*F*	*Sr*	*Pb*
Ca	1.0	0.508	−0.324	0.774†	0.668†	0.861†	0.799†
Fe	—	1.0	0.310	0.710†	0.540	0.613*	0.825†
Cu	—	—	1.0	−0.234	−0.582*	−0.465	0.135
Zn	—	—	—	1.0	0.775†	0.943†	0.869†
F	—	—	—	—	1.0	0.662*	0.861†
Sr	—	—	—	—	—	1.0	0.774†

* Significant correlation at $P = 0.1$.
† Significant correlation at $P \leqslant 0.05$

Table 4 Linear Correlation Coefficients—Section C1

Element	*Ca*	*Fe*	*Co*	*Ni*	*Cu*	*Zn*	*Pb*	*F*	*Sr*
Ca	1.0	0.374	−0.410	0.124	0.563	−0.228	−0.445	−0.691	0.599
Fe	—	1.0	0.933†	0.849†	0.295	0.288	0.356	0.586*	−0.183
Co	—	—	1.0	0.216	0.275	0.277	0.213	0.718*	−0.425
Ni	—	—	—	1.0	0.880	0.890†	0.389	−0.216	−0.062
Cu	—	—	—	—	1.0	0.981†	0.657	−0.269	0.216
Zn	—	—	—	—	—	1.0	0.726*	−0.197	0.158
Pb	—	—	—	—	—	—	1.0	0.852†	0.249
F	—	—	—	—	—	—	—	1.0	−0.583

* Significant correlation at $P \simeq 0.1$.
† Significant correlation at $P \leqslant 0.05$.

Table 5 Linear Correlation Coefficients for Section D2

Element	*Ca*	*Fe*	*Cu*	*Zn*	*Br*	*Zr*
Ca	1.0	0.446	0.728*	0.664	−0.660	0.805*
Fe	—	1.0	0.917†	0.915†	−0.630	0.606
Cu	—	—	1.0	0.985†	−0.759*	0.809*
Zn	—	—	—	1.0	−0.684	0.825*
Br	—	—	—	—	1.0	−0.531

* Significant correlation at $P \simeq 0.05$
† Significant correlation $\simeq 0.01$.

A4 in our notation, where the correlation between calcified material and the iron content is very marked and illustrates the kind of results obtainable.

An immediate feature of all of the line scan results from stone A is the inverse correlation between nitrogen and calcium. This is illustrated in Figure 3B, obtained with section A2 which is of particular interest as it passes through the nidus of the stone. This is at positions 9 and 10 of Figure 3B. The nitrogen concentration at the centre of the stone is in the region of 20% and is expected to be in the form of uric acid or urea.

Stone B. This did not have the concentric structure of stone A. In contrast, it appears to have developed as a granular crystal structure of a calcium oxalate/phosphate mix. The outer layer of the stone, however, shows a thin orange-coloured layer 2 to 3 mm in thickness. From Figure 4 it can be seen that this surface layer contains a large amount of nitrogen and therefore, from the chemical analyses, consists of urea or uric acid, whereas the bulk is calciferous in nature. This indicates a distinct change in material deposition, from calciferous to organic, at a late stage in the development of the stone. The high degree of correlation between Ca and Zn (Table 3) is noteworthy.

Stone C. Figure 5 shows a scan from the outer edge of stone C (position 1) to the central region. This scan shows a very high calcium content (~40%), which points to the presence of hydroxyapatite, as well as calcium oxalate. This correlates well with the chemical analysis.

Stone D. The scan of stone D (Fig. 6) shows that this stone is composed almost entirely of uric acid/urea, with little calcified material. There are, however, regions containing ~0.1% calcium. A noteworthy observation here is the presence of zirconium (Zr). We return to this in the Discussion below.

Discussion

The strong correlation between iron and calcium in section A4 (Fig. 3A) suggests that iron may have a role in calcium oxalate precipitation. This is in conformity with the work of Eusebio and Elliott (1967). It should be noted, however, in table 2, that iron and calcium do not correlate well in section A2. At the nucleus of the stone, iron is present in significant amounts but is associated with a complete absence of detectable calcium. Evidently the presence of iron, though it may facilitate the deposition of calcium, does not necessarily ensure it.

The high concentration of nitrogen at the centre of this stone (Fig. 3B) indicates that the stone probably nucleated as a uric acid stone and that varying amounts of calciferous salts were incorporated into the structure in the course of development.

Other correlations between pairs of elements are observable from these scans. For example, the correlation between zinc and copper (Fig. 3C) is marked and, in additional measurements, correlations between Ca and Cu, and between Ca and Zn, have been demonstrated. The large concentration of calcium at positions 6 and 13 in Figure 3B (also clearly visible in Figure 3A) probably indicates a layer of calcium oxalate formed on the stone at some time after the formation of the stone. This oxalate deposition could be caused by, for example, a temporary rise in pH of the urine, calcium oxalate being insoluble in alkaline solution.

The close correlation between fluorine and lead in stone C (Table 4) may be explained by the fact that they are both known to concentrate in hydroxyapatite. They will therefore appear together in these regions of the stone. The large amounts of fluorine present in the stone may also be significant in the light of work by Anasuya (1982), who demonstrated a correlation between dietary intake of fluorine and the occurrence of urinary calculi in rats, although it is difficult to know the extent to which these findings are applicable to stone formation in humans.

The presence of zirconium—in stone D—is of interest. It is in accordance with some other analyses of urinary stones (McConville, 1982). Zirconium is one of the rarer elements in the diet and in the environment. Its occasional use in the steel industry suggests that it may be present occasionally as an occupational or environmental hazard. The point of interest here is that its presence seems to be confined to the nidus of the stone, where its concentration far exceeds the levels normally found in human tissues and body fluids (Iyengar *et al.*, 1978). Its possible role in stone formation is conjectural, although its presence at the centre of the stone and in no other part of it would seem to point in this direction.

Any discussion of stone formation must take place against a background of detailed work already carried out on stone formation and inhibition. Meyer and Smith (1975) carried out an extensive study of the precipitation of calcium oxalate monohydrate on to seed crystals, and subsequent work (Meyer and Angino, 1977) was directed towards the effect of molecular inhibitors and trace metal ions. The latter were found to have little or no effect on crystallisation in the circumstances of their experiments. Sutor (1969) carried out a great deal of work on growth studies of calcium oxalate in the presence of various added substances with particular reference to inhibition of, or retardation in, crystal growth.

However, Boyce (1968) has developed a matrix theory of stone formation, in which an organic matrix is considered to promote nucleation and calcium oxalate/phosphate crystallisation. Any factor which modifies nucleation in the presence of this matrix will, in principle, promote or inhibit mineralisation; such factors may include the presence of metal ions.

We are thus led tentatively to a general theory of stone formation and development in which trace and minor elements such as Fe, Cu and Zn have a part to play. These elements are known to form complexes of varying solubility with a number of biological molecules. These range from giant proteins to small organic molecules such as uric acid. The study of these complexes is difficult and only limited work has been done so far. The binding of these metals to organic molecules can take place by purely ionic means, but the more stable complexes tend to have some covalent character to their bonding. The Irving–Williams series (Steinhardt and Beychok, 1964) for complex stability

$$\mathrm{Ca(II)} < \mathrm{Mg(II)} < \mathrm{Mn(II)} < \mathrm{Fe(II)} < \mathrm{Co(II)} < \mathrm{Zn(II)} < \mathrm{Ni(II)} < \mathrm{Cu(II)}$$

suggests that complexes involving Fe, Co and Zn may be particularly stable and it is possible that these metal ions could be cross-complexing biological molecules present in the urine (uric acid, urea or proteins) into an *insoluble* phase, thereby promoting stone growth. These elements may be causing flocculations of organic urinary molecules, which then provide the nucleation centres for stone formation and subsequent mineral deposition.

This does not rule out other methods of stone formation, for instance the likelihood of nucleation on to small fragments of tissue and bacterial debris following an infection. More than 1 mechanism may be significant in the formation of stones.

Only a few of the correlations observed in the present work have been discussed here and for further data the detailed compilation by Saint (1985) may be consulted. Sufficient data have, however, been presented to show that the concentration of trace elements in a stone may be markedly different at different stages of development. A degree of correlation between calcium and certain trace and minor elements has been shown. It is clear that the correlations between the several elements detectable by this method of analysis are relevant to the processes taking place during stone formation and growth.

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The Authors

A. Saint, BSc, PhD, Research Fellow, School of Physics, University of Melbourne, Australia.

N A Dyson, MA, PhD, CPhys, MInstP, Senior Lecturer, School of Physics and Space Research, University of Birmingham

Requests for reprints to. N A. Dyson, School of Physics and Space Research, University of Birmingham, P O Box 363, Edgbaston, Birmingham B15 2TT.

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Study of Factors Affecting Calcium Oxalate Crystalline Aggregation

F. GRASES and A. COSTA-BAUZÁ

Department of Chemistry, University of the Balearic Islands, Palma de Mallorca, Spain

Summary—A study was made of the effects of citrate, pentosan polysulphate (a glycosaminoglycan) and mucin (a mucoprotein) upon crystalline growth and aggregation of calcium oxalate in synthetic urine. It was found that citrate inhibited aggregation. Pentosan polysulphate had no perceptible effect on aggregation but favoured the formation of calcium oxalate dihydrate crystals. Mucin enhanced the formation of large characteristic aggregates and also led to the formation of calcium oxalate dihydrate crystals. Particles of mucin in a solution served as a substrate on which several crystals of calcium oxalate dihydrate were formed by heterogeneous nucleation; the subsequent growth of these crystals resulted in the formation of large agglomerates.

Renal calculi have been thought to consist of aggregates of crystalline particles whose size can vary between µm and mm.

The formation of a calculus implies the combination of 2 main steps: crystal nucleation (homogeneous or heterogeneous) and calculus growth. The latter can be explained as a consequence of 2 different processes: crystal growth and its aggregation with others. The importance of aggregation in calculus formation is that it constitutes the most effective and rapid mechanism to increase the size of a particle in a given time.

Thus the aggregation processes can constitute an important risk factor in urolithiasis disease. Some authors have postulated that the organic matrix can play an important role in calculus growth (Pak, 1978; Carmona and Rodriguez, 1987). Others have demonstrated inhibitory properties of a fraction of this organic matrix (Gjalbaek and Robertson, 1980; Lanzalaco *et al.*, 1988). It has also been pointed out that the uromucoid material plays an important part in trapping and agglomerating crystals (Maxfield, 1963; Hallson and Rose, 1979; Rose and Sulaiman, 1982), but others have not yet found a significant relationship between the uromucoid content and aggregation (King, 1967; Haugen *et al.*, 1980). Some authors have postulated that uromucoid excretion increases in non-infected oxalocalcic lithiasic individuals (Boyce *et al.*, 1954; Gale *et al.*, 1966) but others have been unable to confirm this (Thomas *et al.*, 1960; Bichler *et al.*, 1976; Samuell, 1979; Haugen *et al.*, 1980; Sophasan *et al.*, 1980). Moreover, recent studies have demonstrated that urolithiasic individuals excrete a lower level of Tamm-Horsfall mucoprotein than healthy people (Robertson *et al.*, 1984). These results reveal an important controversy on the exact nature of aggregation phenomena. We present new data on the agglomeration processes, their inhibitors and promoters.

Materials and Methods

Reagents, solutions and apparatus. Aqueous solutions of 0.25 M calcium chloride (Panreac) and 0.057 M sodium oxalate (Probus) were used. The following reagents were also used: sodium sulphate (Probus), magnesium sulphate (Panreac), ammonium chloride (Panreac), potassium chloride (Panreac), monosodium phosphate (Panreac), bisodium phosphate (Probus), sodium chloride (Probus), sodium citrate (Probus), pentosan polysulphate, sodium salt (Sigma), mucin from porcine stomach (Sigma). The calcium oxalate dihydrate seed crystals were ob-

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tained according to procedures described by Ackermann *et al.* (1988).

A Kiowa optical microscope provided with a photographic camera and a Hitachi S-530 scanning electron microscope were used for the microscopic observations.

Measurement of agglomeration, crystal size and morphology. The effect of some substances on calcium oxalate crystals aggregation, size and morphology was evaluated in synthetic urine (Table 1), measuring the type and number of particles obtained with a Brand counting chamber and optical microscopy 400 × or using scanning electron microscopy, in the presence and absence of different quantities of the assayed additive, in the following procedures (Table 2).

Experiment 1. In a 1.5 × 10 cm test tube were placed 6 ml of synthetic urine, the additive (pentosan polysulphate or mucin) and 97.4 µl of 0.25 M calcium chloride (final concentration 4.06 mmol/l). The solution was shaken and 112 µl of 0.057 M sodium oxalate (final concentration 1.07 mmol/l) were added. The mixture was then homogenised and maintained at 37°C for 30 min without stirring. The tube was shaken vigorously immediately before the measurement was made and the results were evaluated as above.

Table 1 Composition of Synthetic Urine

Substance	*Conc (mmol/l)*
SO_4^{2-}	10.5
$H_2PO_4^-$	22 2
HPO_4^{2-}	3 0
Cl^-	240.2
Citrate	2.0
Na^+	164.9
NH_4^+	43 4
K^+	81 3
Mg^{2+}	3.0

Table 2 Summary of Experimental Conditions in Final Solutions Used

	$[Ca^{2+}]$ (final conc)	*[Oxalate] *10^3 M*	*[Cit] *10^3 M*	*[P P]^1 (conc range)*	*[Mucin] mg/l*	*$[CaOx]s^2$ mg/l*
Exp 1	4 06	1 07	1 98	0–200	0–200	—
Exp 2	4 06	1 07	0–3 97	—	—	—
Exp. 3	4 23	1 24	1.98	—	200	—
Exp 4	2 3	0.17	1 48	—	0–200	240

(1) [P.P] = [Pentosan polysulphate]
(2) [CaOx]s = [Calcium oxalate dihydrate seed crystals]

Experiment 2. In a 1.5 × 10 cm test tube were placed 6 ml of synthetic urine which contained different quantities of citrate and 97.4 µl of 0.25 M calcium chloride (final concentration 4.06 mmol/l). The mixture was shaken, 112 µl of 0.057 M sodium oxalate (final concentration 1.07 mmol/l) were added and the mixture was homogenised. Incubation and measurement were as described for Experiment 1.

Experiment 3. In a 1.5 × 10 cm test tube were placed 6 ml of synthetic urine, an appropriate volume of the mucine suspension and 101.4 µl of 0.25 M calcium chloride (final concentration 4.23 mmol/l). The solution was shaken and 130 µl of 0.057 M sodium oxalate (final concentration 1.24 mmol/l) were added. The mixture was homogenised and maintained at 37°C for 5 h without stirring and the microscopic observations were then performed.

Experiment 4. In a 1.5 × 10 cm test tube were placed 6 ml of synthetic urine, an appropriate volume of the mucine suspension and 77.4 µl of 0.25 M calcium chloride (final concentration 2.3 mmol/l). The solution was shaken and 24.7 µl of 0.057 M sodium oxalate (final concentration 0.17 mmol/l) were added. The system was homogenised and 2 ml of a suspension 0.001% of calcium oxalate dihydrate seed crystals were added and the homogenisation repeated. The mixture was maintained at 37°C for 5 h without stirring and the microscopic observations were then performed.

All experiments were repeated sufficiently often for the validity of the results to be unequivocal. Photographs were taken for subsequent visual analysis in order to assess the effects of additives on crystal shape and agglomeration.

Results

Figure 1 shows that citrate in Experiment 2 clearly inhibited calcium oxalate crystalline aggregation. Its presence also affected the morphology of the calcium oxalate monohydrate crystals obtained. When the influence of pentosan polysulphate was studied in synthetic urine, no promoting effects on calcium oxalate aggregation were detected (Experiment 1). The effects observed in the presence of a suspension of mucin are shown in Figures 2 and 3. It can be seen that in the presence of mucin in synthetic urine, characteristic large aggregates were

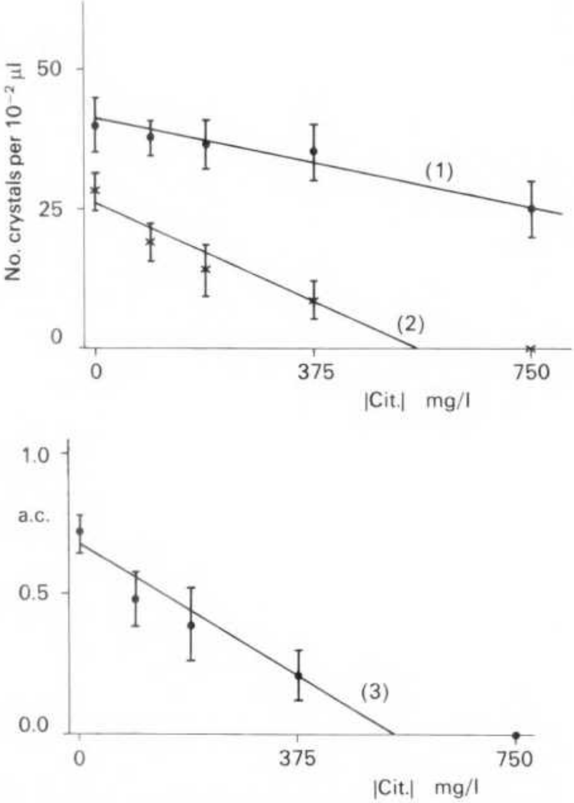
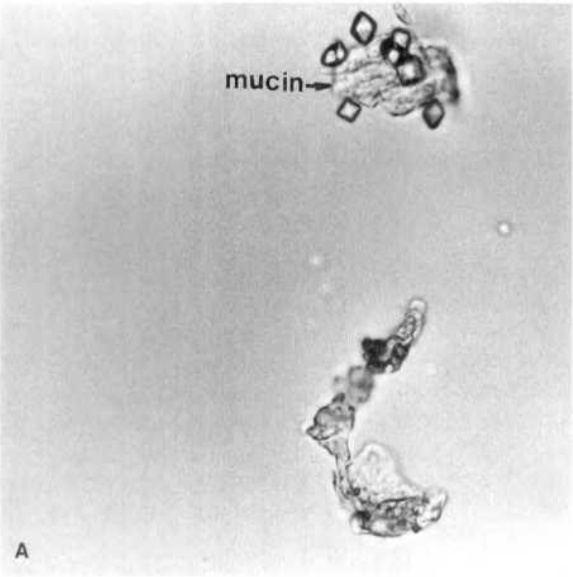


Fig. 1 Quantification of optical microscope measurements. Influence of citrate (Experiment 2). (1) Total crystals observed. (2) Aggregated crystals. (3) Aggregated crystals/total crystals observed. a.c.: aggregation coefficient.



detected. The presence of mucin also favoured the production of calcium oxalate dihydrate. It can be seen from the optical microscope and scanning electron microscope images (Figs 2 and 3) that the mucoprotein material clearly favours heterogeneous nucleation and the formation of crystal aggregates.

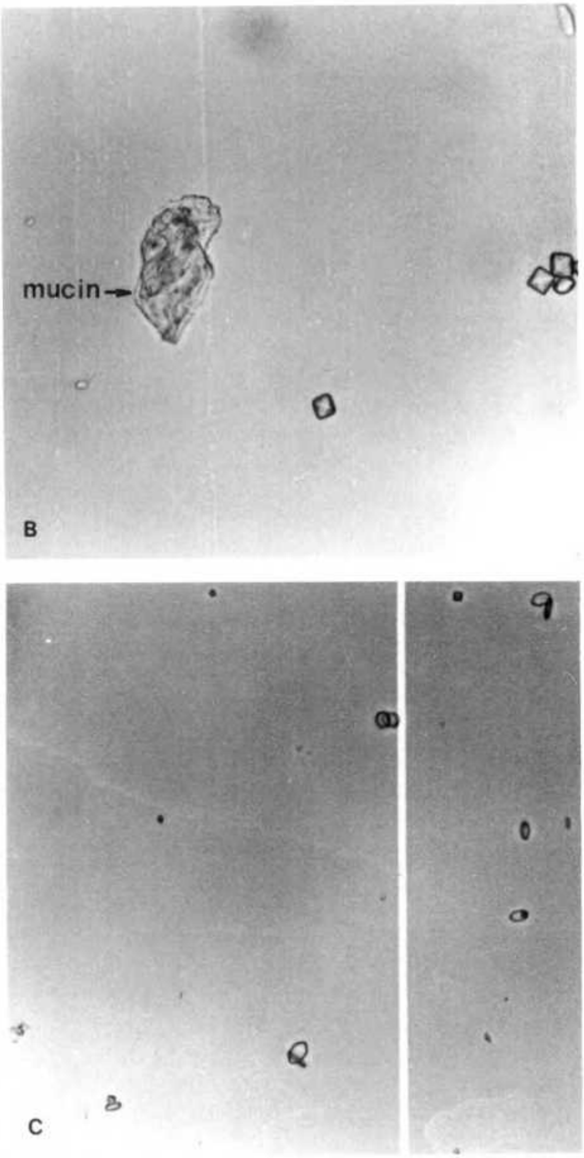


Fig. 2 Optical microscope images (×400) obtained in the presence of mucin (200 mg/l). (**A**) Experiment 3. (**B**) Experiment 4. (C) Optical microscope images (×400) obtained following Experiment 3 but without addition of mucin.

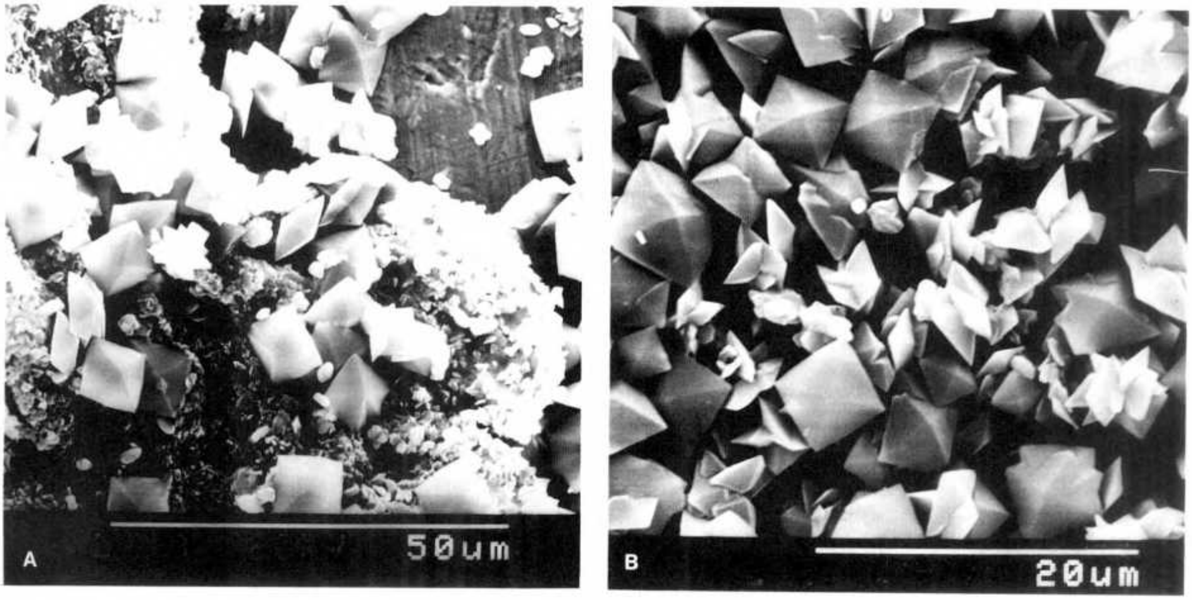


Fig. 3 Scanning electron microscope images obtained in Experiment 3. (A) In the presence of mucin (200 mg/l). (B) Controls without mucin.

Discussion

The study of crystal aggregation processes is of interest in many scientific and technical fields. The kinetics of aggregation can in some cases (in the absence of admixtures) be studied successfully using laser scattering techniques. The greatest difficulty is caused by the influence of admixtures upon the state of aggregation of a resulting product. The latter requires extensive use of the microscope and the results are difficult to quantify. We have shown that some effects can be detected and measured. A study was made of the promoting effects on calcium oxalate aggregation caused by a synthetic glycosaminoglycan (pentosan polysulphate) in the presence of synthetic urine. The results were inconclusive because the changes produced were less than the inherent error of the measurements.

However, the study of a mucoprotein such as mucin showed that it could generate large characteristic aggregates (Figs 2 and 3) when crystallisation of calcium oxalate took place in its presence. On the other hand, mucin also favoured the production of calcium oxalate dihydrate. Thus, as can be seen in Figure 2C, in the absence of mucin, small calcium oxalate crystals (probably monohydrate) were mainly formed. The big crystalline aggregates shown in Figures 2A and 3A were formed in the presence of mucin. The latter formations were not observed when using procedures in which synthetic urine that contained mucin was mixed with calcium oxalate seed crystals (Fig. 2B). This enables us to interpret the crystalline aggregation phenomena as a consequence of the heterogeneous nucleation of several calcium oxalate dihydrate crystals on the same mucin particle (but not as a consequence of the trapping and retaining action of the mucoprotein). We propose a new hypothesis concerning the role of the macromolecular constituents of urine, which accords with the observations of most authors. Thus crystalline aggregation phenomena in urine become difficult to explain when based exclusively on a crystalline trapping and retaining action of the mucoprotein, due to the low crystalline concentration in real urine. Nevertheless, mucoprotein binding to the crystalline surface seems an accepted fact and its inhibitory capacity on crystallisation processes is based on such an event. However, the mucoprotein in a first active step would act as a heterogeneous nucleant, generating a crystalline aggregate. In a second passive step, the mucoprotein would be adsorbed on the crystalline surfaces (inhibition of crystal growth) and thus could act as a heterogeneous nucleant, re-initiating the cycle. Several repititions of such steps would cause renal stones, or at least a significant number of oxalocalcic renal stones.

Citrate, as has been shown by several authors

(Bisac *et al.*, 1978); Curreri *et al.*, 1981; Rose and Hallson, 1984; Grases *et al.*, 1988), manifests inhibitory effects on calcium oxalate crystal growth through binding to the crystal surface. As indicated in the Results section, it was found that the presence of citrate also caused significant changes in the morphology of the calcium oxalate monohydrate crystals formed. Thus, using these experimental conditions and in the presence of citrate, crystals with hexagonal morphology were detected. In its absence, characteristics such as "twin" crystals were observed. Alternatively, as can be deduced from Figure 1, aggregation diminished in the presence of citrate. If it is considered that the presence of citrate at these concentrations did not cause any important changes in zeta potential when synthetic urine was present (Grases *et al.*, 1988), it must be accepted that the inhibitory effects on the aggregation processes cannot be explained in terms of changes in the superficial charge of the calcium oxalate crystals. The data obtained therefore suggest that the geometric structure of the surface is likely to be a potential factor in understanding crystal aggregation.

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The Authors

F. Grases, PhD, Professor, Head of Department of Chemistry.
A. Costa-Bauzá, Graduate, Department of Chemistry.

Requests for reprints to: F. Grases, Department of Chemistry, Faculty of Sciences, University of the Balearic Islands, 07071 Palma de Mallorca, Spain.

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Flexible Cystoscopy as an Adjunct to Extracorporeal Shockwave Lithotripsy

S. D. MARK, J. M. GRAY and W. L. WRIGHT

Department of Urology, Waikato Hospital, Hamilton, New Zealand

Summary—Ancillary procedures associated with extracorporeal shockwave lithotripsy (ESWL) include placement and subsequent removal of double pigtail ureteric stents. A simple new technique has been developed for the insertion of these stents. Using the flexible cystoscope, the procedure is performed on an out-patient basis under local anaesthesia. Placement of the stents was successful in 30/34 patients and removal was successful in 14/14 patients.

The management of renal calculi is now primarily by extracorporeal shockwave lithotripsy (Chaussy and Fuchs, 1989; Kiely *et al.*, 1989; Neerhut *et al.*, 1989). ESWL is available as an out-patient service in Hamilton, New Zealand, using the Wolf Piezolith 2300.

The indications for insertion of double pigtail ureteric stents prior to ESWL are mainly related to stone burden, but also to other factors such as single kidney and ureteric strictures (Fuchs *et al.*, 1985; Riehle *et al.*, 1986). The stents act by causing initial ureteric constriction, then delayed relaxation and dilatation lasting up to 7 days following stent removal (Ramsay *et al.*, 1985). The stents may reduce morbidity (pain, "Steinstrasse", obstructive pyelonephritis, *etc*) and lessen the need for secondary procedures (uretero-endoscopy, insertion of nephrostomy tube). Thus they are an important adjunct to ESWL (Libby *et al.*, 1988; Lingeman *et al.*, 1989). Double pigtail ureteric stents have significant morbidity themselves and their use should be selective (Riehle *et al.*, 1986; Bregg and Riehle, 1989).

Traditional methods of insertion require rigid cystoscopy under general anaesthesia (Smedley *et al.*, 1988). Out-patient flexible cystoscopy has been shown to be time-saving and cost-effective, its role being mainly diagnostic in selecting patients for open or endoscopic surgery (Flannigan *et al.*, 1988; Kennedy and Preminger, 1989). The therapeutic role of flexible cystoscopy includes fulguration of superficial bladder tumours, placement of retrograde ureteric catheters and removal of ureteric stents (Kennedy and Preminger, 1988; Clayman and Kramolowsky, 1986). The availability of a flexible cystoscope, Olympus flexible cystoscopy (C.Y.F.), decreased operating theatre time and pressure for cost-effective practice led to the development of a technique for the placement of double pigtail ureteric stents (Double Pigtail Stent—Cook Urological 7F, Multilength Sof-flex) under local anaesthesia via the flexible cystoscope.

Patients and Methods

Insertion

The operator requires the assistance of a theatre nurse and a radiographer. Antibiotic prophylaxis is used if urinary tract infection is present. Informed consent is obtained and a recent abdominal X-ray reviewed to confirm the site of the renal calculi.

Patients are requested to void and then lie supine on the operating table. The external genitalia are prepared and lignocaine gel (Lignocaine 2% gel with chlorhexidine 0.05%, 10 ml syringe, Delta West Ltd) injected into the urethra. The flexible cystoscope is inserted, the bladder inspected and the appropriate ureteric orifice visualised. The operators rapidly became proficient at identifying the ureteric orifice, finding the view similar to that with the rigid cystoscope. The guide wire (0.038 inch diameter) is inserted up the ureter. A right-handed operator finds insertion into the left ureteric

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orifice easier. Occasionally the right ureteric orifice has to be cannulated with the cystoscope rotated 180°. This is due to the position of the working channel of the Olympus cystoscope at the distal tip.

The guide-wire is passed up the ureter to the level of the kidney and the position confirmed with the image intensifier (Fig. 1). The cystoscope is then removed, leaving the wire *in situ*. Another tube of lubricant lignocaine gel is inserted to facilitate passage of the stent via stent lubrication and opening of the urethra.

The stent is then passed over the guide-wire and its passage can be followed by the image intensifier (Fig. 2).

The stent is positioned with 2 coils in the renal pelvis (Fig. 3), the wire is retracted and the stent is positioned in the bladder (Fig. 4). The guide-wire and pushing device are removed and a plain abdominal X-ray is taken to confirm the position of the stent.

Removal

Informed consent is obtained, the patient is requested to void and lie supine on the bed. The external genitalia are prepared. Lubricant lignocaine gel is injected into the urethra and the flexible cystoscope inserted. Storz flexible grasping forceps (model 27023R) are passed down the working channel and the stent visualised. The stent is grasped more easily at the vesicoureteric junction, where its position is constant. The cystoscope is then removed with the forceps and stent.

Results

Successful placement was obtained in 30/34 patients. The 22 male and 8 female patients had an age range of 22 to 82 years (median 60). The median time for stent placement was 12 min (from when the patient entered theatre until the stent was inserted) and total hospital stay less than 90 min.

Placement was unsuccessful in 4 patients because of inability to feed the stent over the guide-wire up the distal third of the ureter. In 3 patients the stent could not be placed *in situ* under general anaesthesia because resistance in the distal ureter caused the stent to bunch up on the guide-wire, and the procedure was abandoned. No further attempt was made to place a stent in the last patient.

Three of 24 patients returned within 24 h of placement with pain suggestive of renal colic. Two were managed as out-patients with analgesia and 1 patient was admitted. There were no infective complications; 2/24 patients had migration of stents; in 1 case the distal coil migrated into the proximal urethra, necessitating removal; in the other case the stent migrated into the distal ureter, requiring uretero-endoscopic manipulation. Two

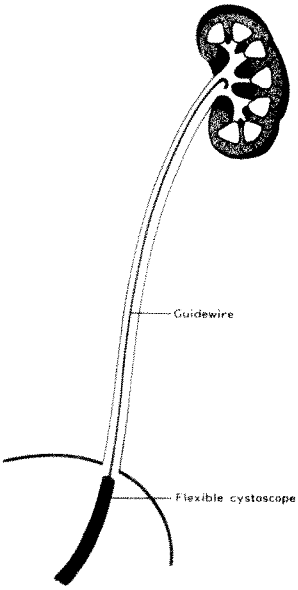

Fig. 1 The flexible cystoscope has been inserted and the guidewire has reached the level of the renal pelvis.

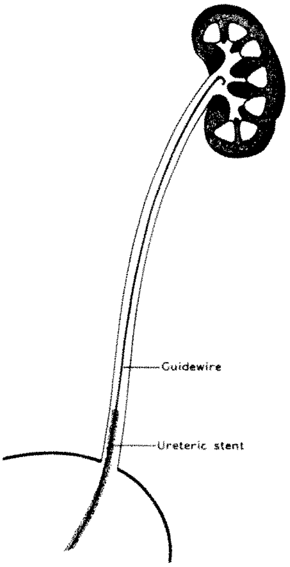

Fig. 2 Ureteric stent being fed over the guidewire.

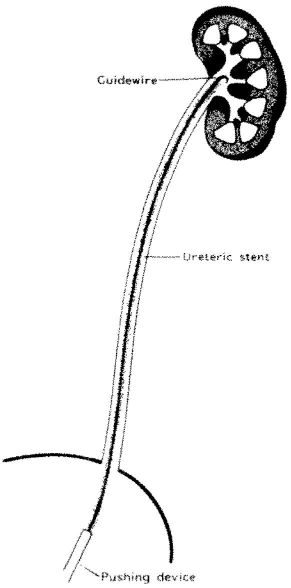

Fig. 3 Ureteric stent positioned in the renal pelvis using the pushing device.

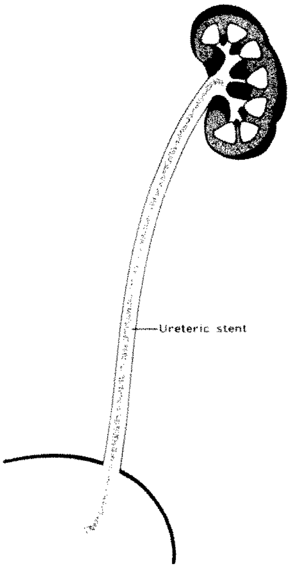

Fig. 4 Ureteric stent *in situ*.

patients required premature removal of the stent for intolerable lower urinary tract irritative symptoms.

In 14/14 patients the stent was removed successfully. The group included 4 females and 10 males with an age range of 22 to 75 years (median 56). The median time for stent removal was 5 min, with a hospital stay of 15 min.

Discussion

A technique is described for the insertion of double pigtail ureteric stents under local anaesthesia, using the flexible cystoscope. The advantage over traditional methods is that general anaesthesia and in-patient treatment are not required. The procedure can be performed in such areas as endoscopy, interventional radiology suites or day-stay operating theatres, due to the requirement of image intensification. Lithotripsy units using X-ray facilities would also be satisfactory.

There is a significant learning curve in using the flexible cystoscope but any operator competent with one should find this technique relatively simple. Two steps are emphasised:

1. The right ureteric orifice can be difficult to cannulate owing to the position of the working channel at the distal tip of the flexible cystoscope. This can be overcome by rotating the cystoscope 180° when attempting to cannulate this side.
2. The need for additional lignocaine gel following removal of the cystoscope prior to inserting the stent. This causes lubrication of the stent on the wire and opens the urethra, leading to less resistance.

In 4 patients this technique was unsuccessful. In 3 patients a further attempt was made to insert the stent under general anaesthesia, but all failed. This was due to obstruction of the passage of the stent at the level of the distal ureter. If the above technique fails, we now perform ESWL without a stent.

The morbidity and mortality rates of general anaesthesia are difficult to quantify. Although low, they will never be without risk (Gibbs, 1984). Thus any procedure performed safely and comfortably under local anaesthesia must lower the risk to the patient.

The cost of this technique was compared with that of a simple 15-min general anaesthetic at the Day-stay Surgical Unit. The cost of the anaesthetic (drugs, anaesthetist and technician) is N.Z. $40.00 and that of a day-stay admission N.Z. $80.00 (Rudge, unpublished data). Thus the total saving for this out-patient local anaesthetic technique is approximately N.Z. $120.00 per patient.

This simple, safe and reliable technique for insertion and removal of double pigtail ureteric stents under local anaesthesia increases the role of the flexible cystoscope in urological practice and complements the Out-patient Lithotripsy Service.

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I thank Sister Lieda Brooks (Charge Nurse, Urology Theatre), Angela for typing the manuscript and Kathy for the illustrations

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The Authors

S D Mark, MB, ChB, Registrar
J M Gray, FRCS, FRACS, Consultant Urologist.
W L. Wright, MB, ChB, FRACS, Consultant Urologist

Requests for reprints to: S D Mark, Department of Urology, Christchurch Hospital, Christchurch, New Zealand.

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Renal Carcinoma in a Solitary Kidney

K. GOHJI, S. KAMIDONO and N. YAMANAKA

Departments of Urology, Kobe University School of Medicine and Shinko Clinic, Kobe, Japan

Summary—We studied the clinical and pathological features of 26 patients with renal carcinoma of a solitary kidney, including 6 treated at this hospital. Four patients had a contracted kidney and 22 had previously undergone nephrectomy. Partial nephrectomy was performed in 16 patients, enucleation of the tumour in 5 and radical nephrectomy in 5 because of the size of the tumour. *Ex vivo* surgery was carried out in 4 patients. The duration of ischaemia ranged from 15 to 365 min but was longer in those who underwent *ex vivo* surgery (149 to 365 min). Of the 21 patients who underwent partial nephrectomy or enucleation, the serum creatinine level increased (≥ 2.0 mg/dl) post-operatively in 16 patients, of whom 9 required temporary haemodialysis. No recurrence has been noted in those who underwent partial nephrectomy, but 1 patient who underwent enucleation of the tumour developed a solitary pancreatic metastasis 2 years 6 months after surgery and was treated by a partial pancreatectomy. Kidney-preserving surgical procedures are considered to improve the quality of life, but careful follow-up is necessary.

Renal carcinoma in a solitary kidney is relatively rare (Novick *et al.*, 1977; Marberger *et al.*, 1981). We present the results of treatment of renal carcinoma in patients with a solitary kidney and the factors influencing their survival.

Patients and Methods

Between January 1981 and March 1989 we treated 6 patients with renal carcinoma of a solitary kidney (Table). The group comprised 5 men and 1 woman ranging in age from 51 to 74 years (mean 63). Two patients had a congenital solitary kidney and the remaining 4 had previously undergone nephrectomy. In 3 patients with stage I renal carcinoma (Robson *et al.*, 1969), nephrectomy had been performed 17 months to 13 years (mean 6 years 3 months) prior to the detection of the new tumour, and in 1 patient for renal calculus 21 years before the detection of the tumour in the remaining kidney. The side affected by the previous illness was left in 4 and right in 2. The 3 patients who had undergone radical nephrectomy for renal carcinoma had no symptoms and the new tumour was discovered on routine follow-up urography or abdominal CT scans. Two patients had asymptomatic macrohaematuria and the tumour was detected on IVU and CT scans. The remaining patient had a palpable abdominal mass which was diagnosed as an abdominal aneurysm, but abdominal CT scan disclosed renal carcinoma. Partial nephrectomy, consisting of removal of the tumour with excision of the rim of the normal adjacent cortex and enucleation were performed in 3 patients (Fig. 1). On histological examination, all of the resected tumours were identified as grade 1 or 2 and stage I or II clear cell carcinoma. The duration of renal ischaemia ranged from 24 to 60 min (mean 38). Temporary renal dysfunction (serum creatinine level ≥ 2.0 mg/dl) was observed in 5 patients for 2 to 18 days post-operatively.

Five patients were free of metastasis for 3 months to 7 years 4 months (mean 2 years 3 months) after treatment, but a solitary pancreatic metastasis was detected in 1 patient $2\frac{1}{2}$ years after enucleation (Fig. 2). He underwent partial pancreatectomy and has been disease-free for 7 months post-operatively. Three patients received intramuscular injections of alpha-interferon.

Between January 1972 and March 1989, 26 patients with renal carcinoma of a solitary kidney (including the 6 treated at this hospital) have been

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Table Summary of Data on 6 Patients with Renal Carcinoma in Solitary Kidney

Case no.	*Age (years)*	*Sex*	*Data on contralateral kidney*	*Main complaints*	*Data on renal ca in solitary kidney*	*Size of resected tumour (cm)*	*Duration of renal ischaemia (min)*	*Complications, peak level of serum Cr, BUN*	*Follow-up*
1	52	M	Lt. nephrectomy (renal ca.), Stage I, Grade 2, 4 years 3 months previously	None	Stage I, Grade 2, enucleation of 2 tumours	0.8 × 0.8 × 0.3 2.8 × 3.0 × 1.5	42	2.0 mg/dl, 25 mg/dl (2 days post-operatively)	Alive 3 years* (recurrence in pancreas)
2	62	F	Lt atrophy (hypoplastic)	Macrohaematuria	Stage I, Grade 1, enucleation	4 × 5 × 5	60	2.9 mg/dl, 31 mg/dl (2 days post-operatively)	Alive 7 years 4 months, free of tumour
3	74	M	Lt. nephrectomy (calculus) 21 years previously	Macrohaematuria	Stage I, Grade 1, partial nephrectomy	3 × 3 × 3	30	2.2 mg/dl, 30 mg/dl (3 days post-operatively)	Alive 2 years 6 months, free of tumour
4	73	M	Rt atrophy (hypoplastic)	None (with abdominal aneurysm)	Stage I, Grade 1, enucleation	2 × 2.8 × 3	34	Post-operative bleeding, 5.2 mg/dl, 57 mg/dl (14 days post-operatively)	Alive 16 months, free of tumour
5	63	M	Lt. nephrectomy (renal ca.), Stage I, Grade 1, 13 years previously	None	Stage II, Grade 1, partial nephrectomy	3 × 3 × 3	24	1.8 mg/dl, 26.1 mg/dl (18 days post-operatively)	Alive 1 year, free of tumour
6	51	M	Rt nephrectomy (renal ca.), Stage I, Grade 1, 17 months previously	None	Stage I, Grade 1, partial nephrectomy (double pelvis)	3 × 3 × 3	36	2.2 mg/dl, 23 mg/dl (2 days post-operatively)	Alive 3 months, free of tumour

* 2¼ years post-operatively, recurrence in pancreas was noted, the metastasitic site was resected. To date he has no evidence of disease. All resected tumours had a fibrous pseudocapsule.

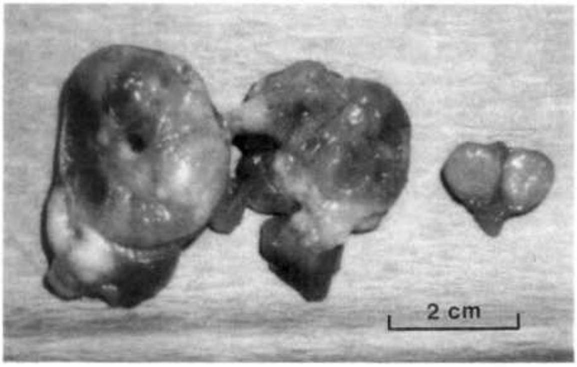

Fig. 1 Enucleation of 2 tumours.

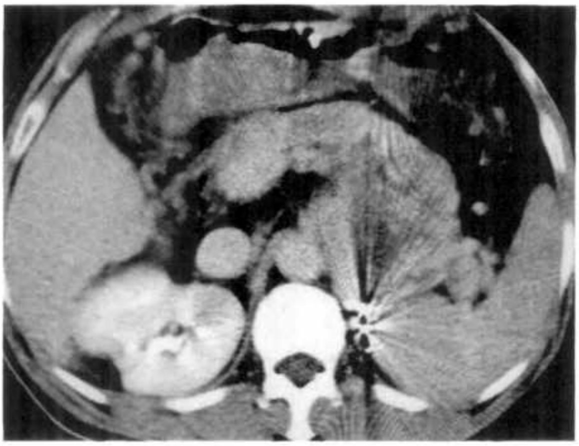

Fig. 2 CT scan showing solitary pancreatic metastasis and deformity of right kidney due to previous enucleation of tumours.

reported in Japan. The age of the 21 men and 5 women ranged from 45 to 74 years (mean 58) (Fig. 3A). The solitary kidney was congenital in 4 patients but the result of previous nephrectomy in the remaining 22. In the latter group, the initial nephrectomy was performed in 10 patients for renal carcinoma 17 months to 24 years (mean 6 years 5 months) previously, in 6 patients for renal tuberculosis 16 to 31 years (mean 27) previously, in 4 patients for renal calculus 21 to 27 years (mean 24 years 3 months) previously, in 1 patient for ureteric tumour 6 years previously, and in 1 patient for unknown reasons 23 years previously (Fig. 3B). Four of 10 patients who had undergone nephrectomy for renal carcinoma were asymptomatic during the present episode and the renal mass was detected during routine follow-up abdominal CT scans. The remaining 4 patients had macrohaematuria and 2 had a palpable mass.

Sixteen patients underwent partial nephrectomy in Japan; the procedure was performed *in situ* in 13 patients and *ex vivo* (bench surgery) with temporary haemodialysis in 3 (Fig. 4A). The tumour was enucleated in 5/26 patients (*in situ* in 4 and *ex vivo* in 1) (Fig. 4A). The 17 tumours resected by the kidney-preserving operation ranged from 0.8 × 0.8 × 0.3 cm to 11 × 10.5 × 8.5 cm. In 5/17 patients the tumour was less than 5 cm in diameter. All of the resected tumours were low grade (1 or 2). The patient who underwent *ex vivo* surgery was treated by temporary haemodialysis. The duration of renal ischaemia ranged from 15 to 365 min, being 149 to 365 min in those who underwent *ex vivo* surgery (Fig. 4B). The mean ischaemic time was 38 min for *in situ* surgery and 256 min for *ex vivo* surgery. Renal function was reduced (serum creatinine ≥ 2.0 mg/dl) in 16 patients, and 9 of these (4 who underwent *ex vivo* and 5 who underwent *in situ* procedures) received temporary haemodialysis. The remaining patient underwent radical nephrectomy with haemodialysis because of a large tumour (Fig. 4A). All patients were followed up for 23 days to 7 years 4 months. Only 1 patient, who had undergone enucleation in this hospital, had a solitary pancreatic metastasis 2 years 4 months after the operation. Two patients died from causes other than cancer (gastrointestinal bleeding and a cardiac accident) and all of the other patients are alive and tumour-free.

Discussion

Renal carcinoma is usually treated by radical nephrectomy. Radical nephrectomy or a kidney-preserving procedure is also performed for bilateral renal carcinoma or renal carcinoma of a solitary kidney (Marberger *et al.*, 1981). In patients with a solitary kidney, however, radical nephrectomy involves post-operative haemodialysis or renal transplantation, which may predispose the patients to other malignancies because of the concomitant immunosuppressive treatment (Novick *et al.*, 1977). Maximum preservation of the kidney should be attempted by procedures such as partial nephrectomy or enucleation of the tumour to ensure a satisfactory quality of life for these patients. Each procedure can be performed either *in situ* or *ex vivo*, with the kidney being excised and autografted after resection of the tumour (bench surgery). The operation is performed more often *in situ* (Zincke and Sen, 1988), but an *ex vivo* procedure is selected when the tumour is located in the middle of the kidney or is surrounded by complex vasculature.

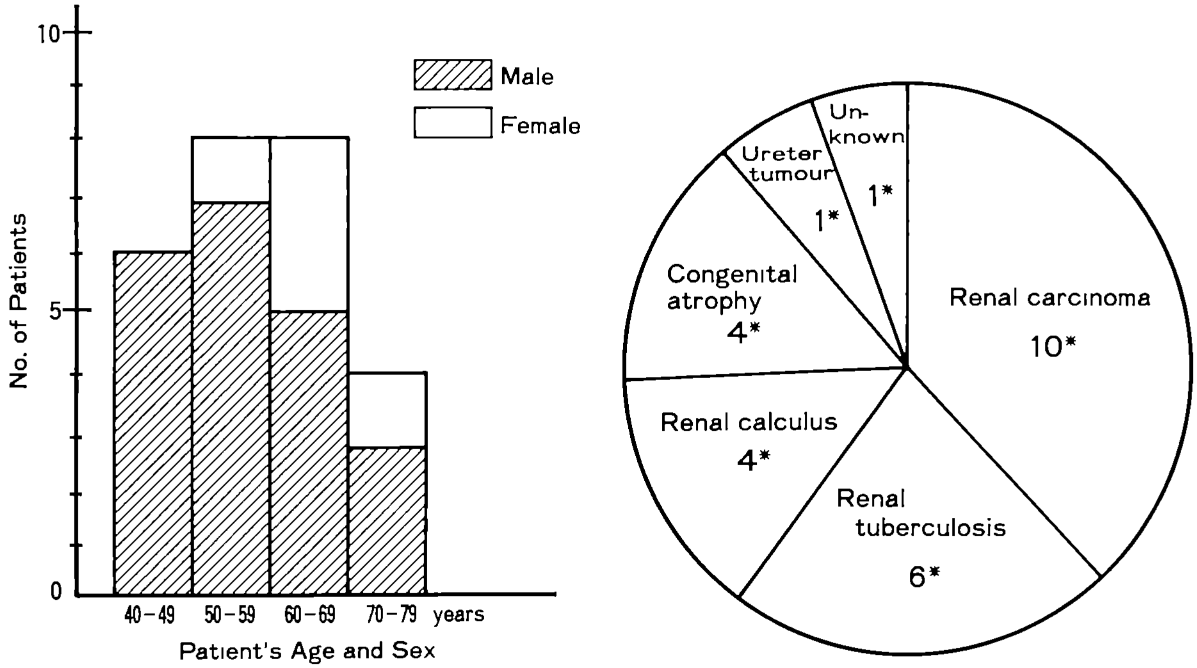

Fig. 3 Patients with renal carcinoma of solitary kidney (A) Age and sex (B) Causes of solitary kidney *Number of patients.

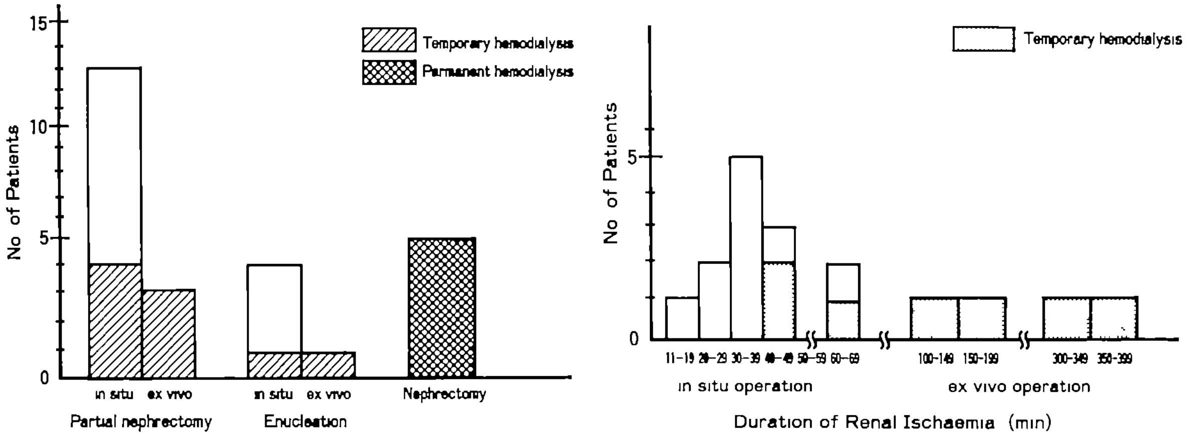

Fig. 4 Patients with renal carcinoma of a solitary kidney. (A) Surgical methods. (B) Duration of renal ischaemia

Smith *et al.* (1984) suggested that *ex vivo* surgery is advantageous in that the procedure provides a wide view and thus allows complete resection of the tumour; it reduces the risk of dissemination, enables extensive dissection of regional lymph nodes and reduces intra-operative haemorrhage. Zincke and Sen (1988) also recommended *ex vivo* surgery. With regard to the disadvantages of this procedure, Smith *et al.* (1984) suggested that it requires complex manoeuvres, including anastomosis of vessels; it is also more time-consuming and likely to damage the renal parenchyma due to ischaemia. For these reasons, the indications for *ex vivo* surgery are limited to the above conditions.

In Japan, *ex vivo* surgery has been reported in 4 patients, but all developed severe renal dysfunction and required temporary haemodialysis. Similarly, Marberger *et al.* (1981) reported an increase in post-operative serum creatinine values in patients treated by *ex vivo* surgery. We performed *in situ* operations in all of our patients. Partial nephrectomy is considered by many to be a useful kidney-preserving procedure in patients with a solitary kidney. Malek *et al.* (1976) examined the survival rate according to the disease of the contralateral kidney. The 5-year survival rates were 69% when renal carcinoma was present in the other kidney and 74% in cases of benign disease; the mean duration of survival was 3.2 and 7.6 years respectively. Similarly, Wickham (1975) reported 5-year survival rates of 37 and 68% for patients with these respective diseases of the other kidney. On the other hand, Topley *et al.* (1984) suggested that the prognosis was worse for non-simultaneous than simultaneous bilateral renal cancer, with 5-year survival rates after partial nephrectomy being 7 and 38% respectively. The 5-year survival rate for simultaneous bilateral renal carcinoma was comparable to that for unilateral renal carcinoma. Zincke and Swanson (1982) also reported 5-year survival rates of 77.8% for simultaneous and 37.5% for non-simultaneous bilateral renal carcinoma. Partial nephrectomy, therefore, is considered to be an effective treatment of renal carcinoma with careful selection of patients. However, small tumours undetectable by CT were reported in 19.7% of patients with renal carcinoma on close macroscopic and histological examination of the kidneys obtained by radical nephrectomy (Mukamel *et al.*, 1988). This indicates the necessity for careful follow-up after kidney-preserving operations.

Enucleation of renal carcinoma is also possible because the tumour is surrounded by a fibrous pseudocapsule. This operation is better than partial nephrectomy because it preserves more renal tissue, facilitates haemostasis and simplifies the surgical procedure (Graham and Glenn, 1979). According to Graham and Glenn (1979), 5 patients with bilateral or solitary renal cancer remained free of recurrence for 9 months to 5 years after this operation. Novick *et al.* (1986) enucleated renal carcinomas in 33 patients with a follow-up period of 9 to 156 months and observed a 3-year survival rate of 90%. Since all of these patients had stage I lesions, they suggested that the procedure was highly effective in selected patients. On the other hand, Marshall *et al.* (1986) attempted *ex vivo* enucleation in the kidneys of 15 patients resected by radical nephrectomy. They reported that the tumours were low grade and encapsulated in 9 patients who showed no residual tumour, but residual tumours such as vascular infiltration, metastasis to regional lymph nodes and extracapsular infiltration, none of which could be detected by CT or other examinations, were noted in 6 patients with high grade tumours. Thus they recommended partial nephrectomy rather than enucleation, as did Blackley *et al.* (1988). Moreover, Marberger *et al.* (1981) reported that renal tumours >7 cm frequently infiltrated the structures at the base of the tumour, and radical removal was frequently achieved. This indicates that kidney-preserving operations should be performed in patients with small tumours. In Japan, enucleation of renal carcinoma has been performed in 5 patients, including 3 of our 6 patients. In 1 of our patients, 2 grade 2 tumours were enucleated. Although this patient showed no local recurrence, pancreatic metastasis was observed 2½ years after the operation and was surgically resected. No recurrence or metastasis has been noted in the other patients who underwent enucleation during follow-up periods ranging from 28 days to 7 years 4 months. All patients who underwent partial nephrectomy were free of recurrence for 3 months to 2½ years after surgery. Marberger *et al.* (1981) reported that the survival of patients treated by kidney-preserving operation correlated local tumour spread, grade and diameter of the tumour, *i.e.* vascular invasion, high grade, large tumour and spindle cells indicated a poor prognosis. With regard to the patient's quality of life after the operation, we consider, as do Malek *et al.* (1976), Novick *et al.* (1977), Marberger *et al.* (1981), Marshall and Walsh (1984) and Marshall *et al.* (1986), that partial nephrectomy or enucleation of the tumour is an excellent kidney-preserving operation for low grade and small renal tumours in patients with a solitary kidney. However, careful follow-up is essential.

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The Authors

K Gohji, MD, Senior Lecturer, Department of Urology, Kobe University School of Medicine.

S Kamidono, MD, Professor and Chairman, Department of Urology, Kobe University School of Medicine.

N. Yamanaka, MD, Consultant Urologist, Shinko Clinic

Requests for reprints to · K. Gohji, Department of Cell Biology, Box 173, University of Texas, M D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030, U.S.A

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Use of the Double Pigtail Stent in Stone Retrieval following Unsuccessful Ureteroscopy

B. J. JONES, P. C. RYAN, O. LYONS, R. GRAINGER, T. E. D. McDERMOTT and M. R. BUTLER

Department of Urology, Meath Hospital, Dublin, Ireland

Summary—Insertion of a double pigtail stent is known to cause ureteric dilatation. We analysed the effect of an indwelling double pigtail stent on the success rate of calculus extraction by second ureteroscopy when the initial ureteroscopy fails. Over a 12-month period, a first ureteroscopy failed in 42 patients; 30 were then treated by ureteroscopy combined with a ureteric stent and 12 were treated without a ureteric stent. The group with an indwelling stent had a successful second ureteroscopy or spontaneously passed the calculus in 24 cases (84%) compared with 5 unstented cases (45%). Ureterolithotomy was necessary in 2 patients with a stent and 3 with no stent. It was concluded that following failed ureteroscopic manipulation of calculi, insertion of a double pigtail stent was associated with a higher subsequent success rate for removal of stone by ureteroscopy and a consequent lower rate of ureterolithotomy.

The double pigtail stent has proved useful in the management of ureteric obstruction (Hepperlen *et al.*, 1978) and injury (Lang, 1981). After unsuccessful ureteroscopy for a ureteric calculus, an *in situ* double pigtail stent will drain an obstructed upper urinary tract despite the continued presence of the calculus. Stents cause ureteric dilatation (Drake *et al.*, 1962; Weinberg, 1975) and may facilitate subsequent ureteric instrumentation (Perez-Castro and Martinez-Pinero, 1982). The purpose of this study was to investigate the effect of an indwelling double pigtail stent on the success of subsequent ureteroscopic manipulation of calculi following an initial failure.

Patients and Methods

A retrospective analysis was performed of all failed ureteroscopies in patients with ureteric calculi from July 1987 to July 1988. There were 42 failed ureteroscopies from a total of 288 examinations of patients for stones. The instrument of choice was either a 9.5 or an 11 F rigid ureteroscope manufactured by Richard Wolf. The outcome was assessed by the number of stones retrieved and radiographic evidence of stone removal. The stents were 5 to 7 F polytetraflourethylene made by Cook Urological Incorporated. We studied the small incidence of morbidity due to indwelling stents, noting events such as ureteric perforation or sepsis. Patients often suffer vesical and renal pain from the presence of an indwelling double pigtail stent but the incidence of this particular problem was not analysed.

Results

Of the 42 patients in whom the first ureteroscopy was a failure, 30 were managed with and 12 without a double pigtail stent. The male:female ratio was similar for both groups (18:12 and 7:5 respectively). The mean age for both groups was 42 and 38 years respectively. The calculus size was similar in both groups (Table 1). Failure was judged by inability to remove a calculus and was usually due to failure to advance the ureteroscope to the level of the calculus (Table 2). This was due most often to poor visualisation in the presence of haemorrhage or failure to advance the ureteroscope in a tight distal ureter.

The results of treatment are shown in Table 3.

Based on a Poster Demonstration at the 45th Annual Meeting of the British Association of Urological Surgeons in St Helier, June 1989

Table 1 Mean Calculus Diameter and Distribution along the Ureter

	Mean diameter (mm)	*Upper ureter (%)*	*Middle ureter (%)*	*Lower ureter (%)*
Stented (n = 30)	9	18 (60)	7 (23)	5 (17)
Unstented (n = 12)	7.4	7 (58)	3 (23)	2 (17)

Table 2 Reasons for Failure of First Ureteroscopy

	Failure to pass scope to stone	*Stone not visualised*	*Unable to manipulate*
Stented (n = 30)	25	2	3
Unstented (n = 12)	6	2	4

Table 4 Complications

	Ureteric perforation	*Hung basket**	*Urinary tract infection*
Stented (n = 30)	2	1	4
Unstented (n = 12)	2	1	2

*Calculus and basket engaged at intramural ureter but extraction not possible

There was a significant difference in the success rate of the second ureteroscopy when patients were stented: 21 of 30 patients in the stented group had a successful second ureteroscopy compared with 5 of 12 patients in the unstented group ($P = 0.015$, Fisher's two-tailed exact probability test). Of the 16 failures a third ureteroscopy was successful in 4 patients from each group. Two patients (6.6%) in the stented group required ureterolithotomy compared with 3 (25%) in the unstented group ($P < 0.1$, χ^2 analysis). The size of the stones in patients requiring ureterolithotomy was comparable for both the stented and the non-stented patients.

Three patients with an indwelling stent passed their calculus spontaneously; no patient in the unstented group did so.

The complication rate is shown in Table 4.

Discussion

The double pigtail stent is a versatile device. It allows the obstructed or injured ureter to be defunctioned endoscopically and this has led to its widespread adoption by many urologists. An indwelling stent or catheter causes reversible ureteric dilatation (Wiseman, 1934) but the mechanism by which this occurs has not been elucidated, although physiological relaxation and direct cytotoxic effects have been suggested (Drake *et al.*, 1962).

The results of this study show that inserting a double pigtail stent after an unsuccessful attempt at removing a ureteric calculus by ureteroscopy has 2 effects; it increases the likelihood of extraction at a second attempt and relieves obstruction due to the stone. In 70% of cases an indwelling stent facilitated the passage of the ureteroscope at the second attempt. In addition, insertion of a double pigtail stent was associated with spontaneous passage of the calculus in 3 cases.

In this study the ureteric stent was retained for periods ranging from 2 to 4 weeks, but the time taken for dilatation to occur and thus improve the success rate of ureteroscopy was not fully established. Where stents were used the ureterolithotomy rate was lower (6.6% versus 25%). A total of 5 ureterolithotomies in 42 failed cases indicates that there is a small but continuing role for open surgery. The complication rate in both groups was acceptably low. Data were not available, however, on the incidence of pain due to indwelling stents. This can be severe in some cases and restricts the use of stents to situations where they are essential to facilitate ureteroscopy.

When ureteroscopic manipulation fails to extract a stone, insertion of a double pigtail stent allows drainage of the obstructed upper urinary tract. This study has shown that an indwelling double pigtail stent facilitates the passage of the ureteroscope and subsequent extraction of the calculus. Spontaneous passage of the stone is an added bonus, obviating the need for subsequent manipulation. We recommend that in the event of unsuccessful ureteroscopy to remove a ureteric calculus a double pigtail stent

Table 3 Results

	Successful 2nd ureteroscopy (%)	*Successful 3rd ureteroscopy (%)*	*Uretero-lithotomy (%)*	*Spontaneous passage (%)*
Stented (n = 30)	21 (70)	4 (13)	2 (6.6)	3 (10)
Unstented (n = 12)	5 (42)	4 (33)	3 (25)	0

should be inserted, followed by further ureteroscopy.

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The Authors

B. J. Jones, FRCSI, Registrar in Urology
P. C Ryan, FRCSI, Senior Registrar in Urology, Mater Misericordiae Hospital, Dublin.
O. Lyons, MB, BCh, BAO, Senior House Officer.
R Grainger, FRCSI, Consultant Urologist.
T E. D. McDermott, FRCSI, Consultant Urologist.
M R. Butler, FRCS, FRCSI, Consultant Urologist.

Requests for reprints to: B J. Jones, Department of Urology, Meath Hospital, Dublin 8, Ireland

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Effects of Acid-base Changes on Human Ureteric Smooth Muscle Contractility

R. S. COLE, C. H. FRY and K. E. D. SHUTTLEWORTH

Department of Urology, St Thomas' Hospital; Department of Physiology, St Thomas' Hospital Medical School, London

Summary—Wide fluctuations of both urinary pH and the partial pressure of CO_2 (PCO_2) occur in normal physiological circumstances and in a variety of pathological conditions. However, the effect of extracellular pH on the contractility of human ureteric muscle has not been clearly defined.

This study has established, using a microsuperfusion technique, that an increased superfusate PCO_2 increases the magnitude of the phasic contraction to electrical field stimulation. A similar extracellular acidosis induced by alteration of the $[HCO_3^-]$, at constant $[Na^+]$ and free $[Ca^{2+}]$, was without significant effect. Furthermore, when both superfusate PCO_2 and $[HCO_3^-]$ were simultaneously increased at constant pH the contractile response was similar to that when PCO_2 alone was raised.

These observations suggest that the changes of tension were mediated by intracellular pH changes, providing it is assumed that the ureteric smooth muscle cell membrane is permeable to CO_2 but impermeable to H^+ and HCO_3^-. The occurrence of an increase of force in the presence of an acidosis is a highly significant and unusual finding, since it has been assumed that the classical association between acidosis and negative inotropy, seen in cardiac muscle, was also applicable to smooth muscle.

Since the first *in vitro* studies of ureteric function appeared about 1900, no systematic analysis of the influence of acid-base changes upon ureteric smooth muscle contractility has been made, although spontaneous contractions have been studied in various muscle bath solutions ranging from pH 5.6 to 8.4 (Boyarsky and Labay, 1972). Roth (1917) considered that Locke's solution with pH 8.1 to 8.3 was best suited for eliciting maximal spontaneous contractions and rhythmicity of animal ureters. Decreasing pH was associated with a lowering of tone and rhythmicity. Macht (1917) maintained that an increase in the pH of the muscle bath decreased the activity of animal ureters and a decrease in pH markedly increased tone and the rate of contraction.

The contractile response of human ureteric smooth muscle to changes of extracellular pH is important for several reasons. Firstly, the pH of normal urine may vary between pH 4.5 and 8.0. Similarly, the partial pressure of CO_2 (PCO_2) in urine fluctuates over a wide range. Strassburg (1872) first recognised that the PCO_2 of freshly voided urine from the dog was greater than that of plasma, with a mean value of 70 mm Hg (range 56–84). Since then, others have confirmed the high levels of CO_2, using either direct methods (Sendroy *et al.*, 1934), or indirectly by calculation from the Henderson-Hasselbalch equation and measuring pH and total CO_2 (Gamble, 1922). In general, the PCO_2 seems to correlate best with urine pH, high values occurring in alkaline diuresis and lower values (although still higher than plasma) following ingestion of ammonium chloride solution (Hong *et al.*, 1960). Furthermore, urine PCO_2 varies inversely with urine flow in humans (Ryberg, 1948) and dogs (Kennedy *et al.*, 1952). The latter group also demonstrated a direct relationship between urine

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PCO_2 and buffer concentration of the urine. In addition, Pak Poy and Wrong (1960) found that in certain patients with a variety of renal tubular disorders (renal tubular acidosis, Na-losing nephropath and adult Fanconi syndrome), urinary PCO_2 was low, approximating to that of plasma. Patients with chronic unilateral pyelonephritis, predominantly affecting tubular cells, were noted to have a significantly lower PCO_2 in urine from the diseased kidney compared with the healthy kidney (Koch *et al.*, 1972).

Although the transitional cell epithelium lining the urinary tract is considered to form an impermeable protective barrier to urine, there is considerable evidence that CO_2 can diffuse rapidly across cell membranes (Jacobs, 1920). There is also evidence to suggest that calculus disease of the urinary tract and infection may damage the protective nature of the epithelium, allowing the smooth muscle cells to be exposed to urine directly (Fussel and Roberts, 1979). The presence of urinary infection may in itself lead to considerable changes of urinary pH, via the urease splitting properties of certain pathogenic bacteria, in particular *Proteus*, *Pseudomonas*, *Klebsiella* and some strains of *Staphylococcus*. Infection has been used to explain the non-obstructive dilatation of the upper urinary tract associated with acute pyelonephritis (Kass *et al.*, 1976) and infective staghorn calculi, but as yet any accompanying pH changes have not been incriminated in the aetiology. Thus it might be proposed that changes of urinary PCO_2 occur during obstructive or infective conditions which might alter ureteric function.

We have therefore studied the effects of acute acid-base changes on the contractility of human ureteric smooth muscle strips and found that intracellular acidosis increased the force of contraction whilst extracellular acidosis was without effect. Some of the results have been communicated to the Physiological Society (Cole and Fry, 1987).

Materials and Methods

Small circular strips of muscle (2 × 0.5 mm) were dissected from segments of human ureter discarded at routine urological operations. These were mounted in a muscle bath and superfused with a modified Tyrode's solution at 36°C which was equilibrated with 95% O_2/5%CO_2. The measured pH of the superfusate was 7.36 ± 0.01 (SE of mean, n = 17). The composition of the Tyrode's solution was: NaCl, 118 mM; KCl, 4 mM; $NaHCO_3$, 24 mM; NaH_2PO_4, 0.4 mM; $MgCl_2$, 1 mM; $CaCl_2$, 1.8 mM; glucose, 6 mM; Na pyruvate, 5 mM. One end of the muscle preparation was tied to a fixed hook in the floor of a superfusion trough and the other end to an isometric force transducer (Statham UC2, Oxnard, USA). The preparations were not spontaneously active and were field stimulated every 50 s by single electrical square pulses of 10 to 40 ms duration via platinum plate electrodes embedded in the wall of the trough. The consequent isometric contractions were displayed on a moving paper chart recorder via a bridge amplifier (Fig. 1).

Extracellular pH was altered by changing either the superfusate PCO_2 or [$NaHCO_3$]. The PCO_2 was altered by equilibrating the superfusate with gas mixtures containing 2, 10, 20 or 30% CO_2—the remainder made up with O_2. In order to ascertain that any contractile changes were not due to alteration of superfusate PO_2 a further gas mixture was used in which N_2 was a partial replacement for

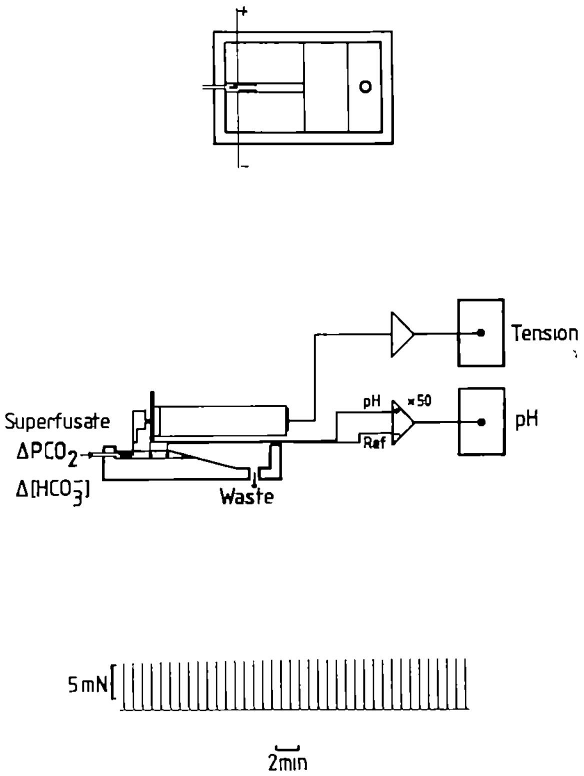

Fig. 1 Top panel: aerial view of muscle bath. Middle panel. diagrammatic representation of the recording apparatus, showing the preparation and isometric force transducer. Bottom panel: the consistent contractile response of the preparation to electrical stimulation Single shocks, 20 ms duration, applied once every 50 s at supramaximal voltage. Temperature 36°C.

O_2—5% CO_2, 70% O_2, 25% N_2. A change of superfusate pH at constant PCO_2 was accomplished by varying the [$NaHCO_3$] between 6 and 48 mM. The [Na] was constant by equimolar addition or replacement of NaCl. HCO_3^- and Ca^{2+} form ion pairs in solution, reducing the free [Ca^{2+}]. The free [Ca^{2+}] was kept constant by varying the [$CaCl_2$] as the [$NaHCO_3$] was altered (Fry and Poole-Wilson, 1981), the composition is given in Table 1. In a further series of experiments the superfusate PCO_2 and [$NaHCO_3$] were both raised at constant pH and contained 48 mM $NaHCO_3$ and equilibrated with 10% CO_2/90% O_2. The composition and pH values of the various superfusates are shown in Table 1.

The superfusate pH was continuously monitored with a dip-cast plastic H^+-selective electrode (Fry *et al.*, 1984) placed in the superfusion trough downstream from the muscle. A streaming 3M KCl filled bridge placed beside the H^+-selective electrode served as the reference electrode (Fig. 1). The H^+-selective electrode was calibrated with standard buffer solutions (Radiometer, Copenhagen, Denmark) flowing through the superfusion trough.

Results

The consistent phasic contractions of the muscle preparation in response to electrical field stimulation served as an excellent control parameter by which the effects of extracellular pH changes on ureteric contractility were measured (Fig. 1). The contractile response of the muscle preparation to electrical field stimulation was markedly and consistently influenced by the superfusate PCO_2.

A typical response to an extracellular acidosis (pH 6.8) induced by increasing the CO_2 of the equilibrating gas mixture from 5 to 30% is illustrated in Figure 2. The acidosis is recorded by the H^+-selective electrode and seen in the lower trace. Phasic tension increased, reaching a maximal value within 6 contractions and was followed by a partial recovery. On return to the control solution, the contraction returned to the control value with a similar time course.

In the experiment illustrated in Figure 3 the superfusate PCO_2 was incrementally raised by raising the CO_2 content of the equilibrating gas mixture to 10, 20 and 30% (parts a–c). In the final panel (part d) the PCO_2 was reduced by using a 2% gas mixture. The lower trace in each panel again shows the superfusate pH and the upper trace phasic contractions. The traces show a positive correlation between the magnitude of the acidosis and the increase of force; a reduction of force with an alkalosis was also observed.

A summary of a number of similar experiments is shown in Figure 4, in which the force of contraction is plotted as a function of superfusate pH as a result of changing PCO_2. Tension has been expressed as a percentage of that developed in normal Tyrode's solution at pH 7.36. The line is a best fit of an exponential function through the data points, but has no special significance. It is evident that over the entire range of pH values from 7.8 to 6.8, decreasing superfusate pH increased the force of contraction. When compared with control, acidosis was more effective in altering tension than a comparable alkalosis.

A possible explanation for the alteration of muscle function may be a change of the superfusate PO_2 rather than a variation of PCO_2 and pH, because changes in the CO_2 content of the equilibrating gas mixture were obtained at the expense of the O_2 content. This possibility was discounted by experiments in which N_2 was used as a neutral

Table 1 Composition and Measured pH Values of the Different Superfusates.

NaCl (mM)	*$NaHCO_3$ (mM)*	*$CaCl_2$ (mM)*	*CO_2 (%)*	*O_2 (%)*	*N_2 (%)*	*pH*	*n*
142	24	1.80	5	95	0	7 36±0 01	17
142	24	1.80	2	98	0	7 80±0 05	13
142	24	1 80	10	90	0	7 21±0.01	24
142	24	1 80	20	80	0	6.98±0 02	20
142	24	1.80	30	70	0	6 83±0.01	17
142	24	1.80	5	70	25	7 36±0 02	5
136	6	1 50	5	95	0	6 78±0.04	14
130	12	1 58	5	95	0	7.12±0 02	14
94	48	2.45	5	95	0	7.67±0 03	19
94	48	2.45	10	90	0	7 37±0 01	10

Mean values (±SE of mean) and the number of determinations (n) are shown

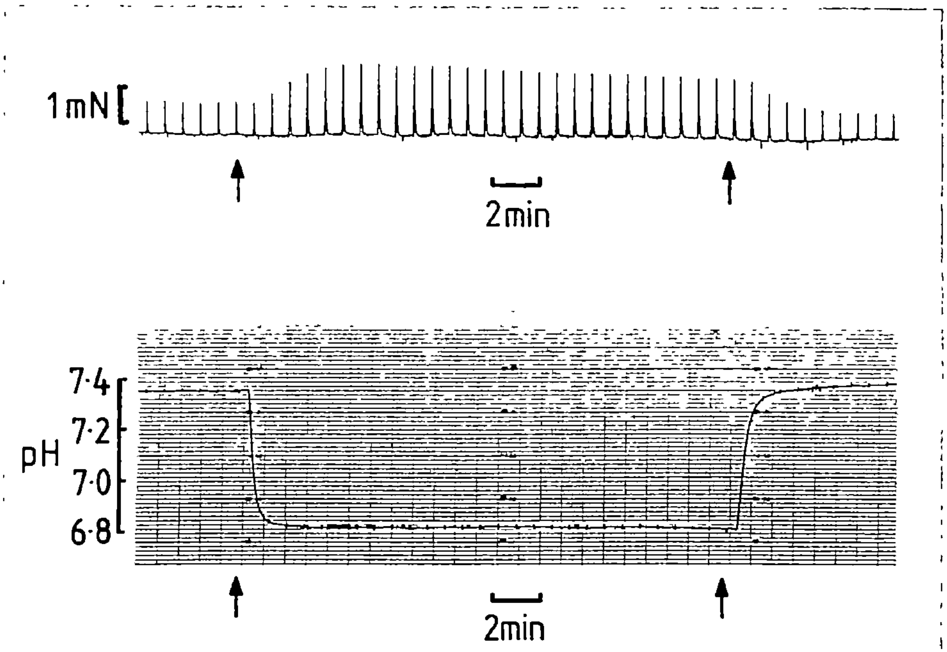

Fig. 2 The response to extracellular acidosis by increasing superfusate PCO_2. Upper trace, isometric force, lower trace, superfusate pH The arrows mark the intervention CO_2 content of the equilibrating gas mixture was raised from 5 to 30% Temperature 36°C.

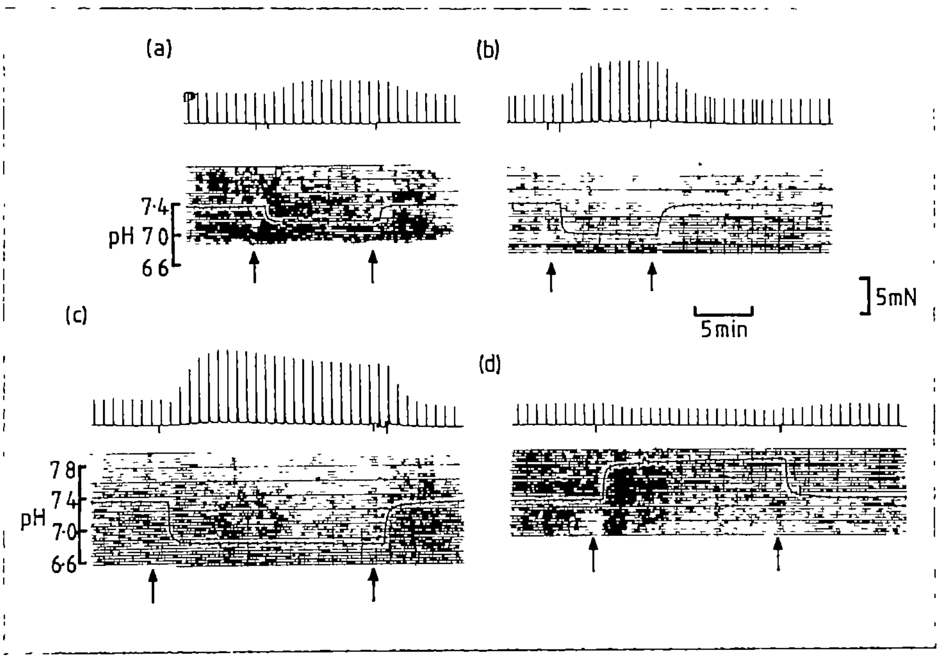

Fig. 3 The response to variable alteration of superfusate PCO_2. CO_2 content of equilibrating gas mixtures changed from 5% to 10%, 20%, 30% and 2% in panels a–d respectively. Upper traces, isometric force, lower traces, superfusate pH Temperature 36°C.

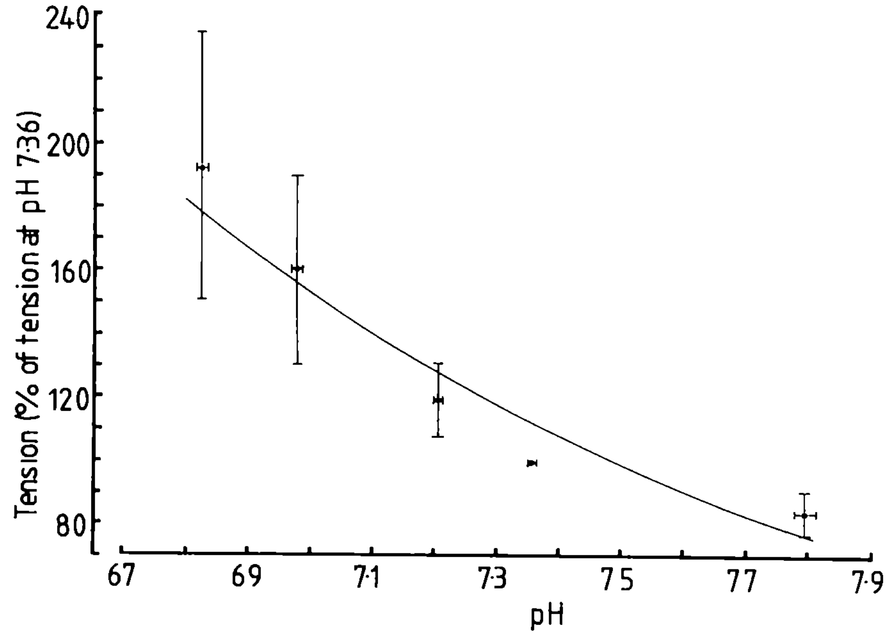

Fig. 4 The relationship between superfusate pH and steady state phasic tension Tension is expressed as a percentage of that measured in control solution, pH 7.36. Superfusate pH was altered by varying PCO_2 Error bars represent SD of an observation, n=13 pH 7 8, n=24 pH 7.2; n=20 pH 7 0, n=17 pH 6 8 Temperature 36°C.

replacement for part of the O_2 content, at a constant CO_2 percentage. In order to reflect the greatest degree of hypoxia inflicted on the preparation a gas mixture consisting of $5\%\ CO_2/25\%\ N_2/70\%\ O_2$ was equilibrated with the superfusate—the pCO_2 and pH of this solution were not different from the control superfusate (Table 1). Equilibration of the superfusate with this gas mixture gave contractile responses identical to those of the control solution, so that it is unlikely that changes in the superfusate PO_2 contributed to the above contractile changes.

There is considerable evidence that CO_2 equilibrates more rapidly than HCO_3^- or H^+ over the cell membrane (Jacobs, 1920), so that an intracellular pH change may account for the alteration in the force of the phasic contractions in response to changes in superfusate pH. Therefore a further series of experiments was performed at constant PCO_2 in which superfusate pH was altered by changing the $[HCO_3^-]$ (Table 1). The results are summarised in Table 2 and are less consistent than those obtained when superfusate PCO_2 was changed.

In a total of 43 separate interventions in which extracellular acidosis was induced, a small increase in isometric tension was observed in 15 cases and a small decrease was seen in 20 (range +36% to −32%). Figure 5 shows a typical experiment in which the muscle was exposed to a solution containing 6 mM $NaHCO_3$, at pH 6.8. The superfusate pH is again shown in the lower tracing and the contractile response in the upper trace. Over a period of 35 min there was little change of force. When the muscle strips were exposed to an alkalotic superfusate, containing a raised $[NaHCO_3]$, developed tension increased in 24 of 29 interventions and decreased in the remaining 5 (range +8% to −32%).

These results suggest that the permeability of the ureteric smooth muscle membrane to H^+ or HCO_3^- is low and that alterations to intracellular pH are responsible for the observed changes to contraction.

Table 2 Responses of Ureteric Muscle to Alterations of Superfusate pH by Alteration of the $[NaHCO_3]$ at Constant PCO_2

Superfusate pH (mean ± SE of mean)	*Tension (% of control Tyrode's solution pH 7.36, mean ± SE of mean)*
6.78±0.04	+ 1.5±15.9 (n=14)
7 12±0.02	+ 2 3±13 3 (n=14)
7 67±0 03	+17.5±28.1 (n=19)

n=number of preparations

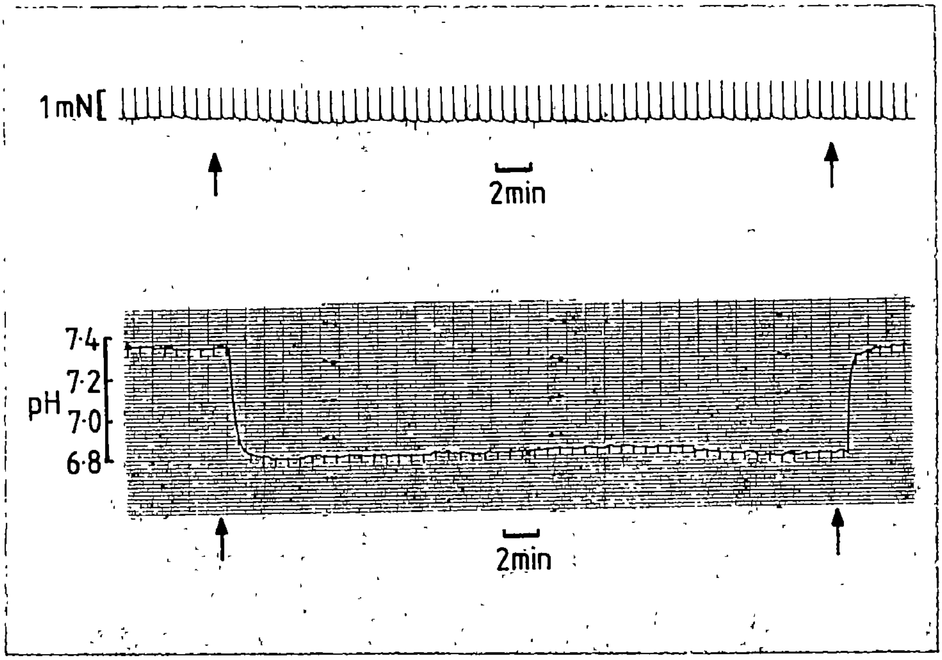

Fig. 5 The response to acidosis by decreasing superfusate [$NaHCO_3$] from 24 to 6 mM at constant PCO_2. Upper trace, isometric force; lower trace, superfusate pH. Temperature 36°C.

This hypothesis was further supported by the experiment illustrated in Figure 6. In this example superfusate PCO_2 and [$NaHCO_3$] were both doubled in order to keep superfusate pH constant.

A rapid and reversible increase in tension was observed with a time course and magnitude similar to that observed when PCO_2 alone was doubled, indicating that CO_2 diffused into the cell sarcoplasm and acidified this compartment, thus causing the contractile change. It will be noted that at long times there was a small secondary decline of force which might represent a smaller and slower passage of H^+ and HCO_3^- across the cell membrane or a reduction of superfusate PCO_2 during the intervention. However, the interventions in such experiments were considerably longer (mean 1024 s, range 250–3940) than those in which PCO_2 alone was altered (mean 303 s, range 230–420), as in Figures 2 and 3, so that a similar phenomenon may not always have been evident.

Discussion

The results presented in this study show that an extracellular acidosis, induced by raising the PCO_2 of the superfusate, increased the phasic component of contraction in a ureteric muscle strip. Similar alterations to extracellular pH by altering the [$NaHCO_3$] were without effect. These observations show that force modulation may result from

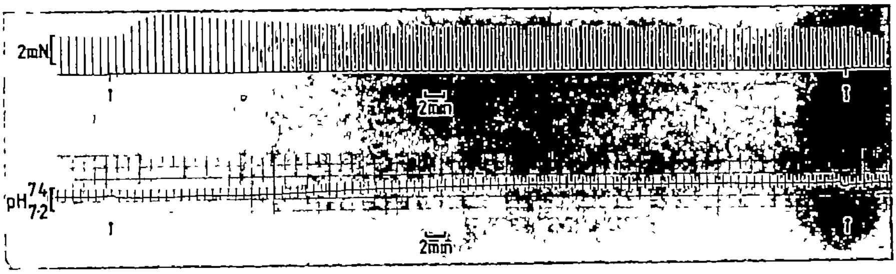

Fig. 6 The response to simultaneous increase of superfusate PCO_2 and [$NaHCO_3$]. Upper trace, isometric force; lower trace, superfusate pH Temperature 36°C

intracellular pH changes rather than extracellular changes if it is assumed that the muscle membrane is permeable to CO_2 but not to H^+ and HCO_3^-. This hypothesis was further strengthened by the fact that increasing extracellular PCO_2 and $[HCO_3^-]$ by the same proportion, thus keeping extracellular pH constant, caused the same changes in force as raising the PCO_2 alone. No direct measurements of intracellular pH have been made in this preparation, but, in isolated ferret detrusor muscle cells Baro *et al.* (1989) measured intracellular pH with epifluorescence microscopy and confirmed that increasing extracellular PCO_2 did acidify the cell interior whilst changes to the $[NaHCO_3]$ had a much smaller effect.

Although it has been widely assumed that the classical association between acidosis and decreased cardiac contractility was also applicable to smooth muscle, it has recently emerged that certain types of smooth muscle produce increased force during intracellular acidosis (Wray, 1988). This diversity of response is exemplified by vascular smooth muscle. It has long been established that the main regulator of cerebral blood flow is the direct action of CO_2 on the intracellular pH of vascular smooth muscle cells in vessels supplying the brain; the fall of intracellular pH leads to vasodilatation and an increased blood flow to the brain. Similarly, Garnier and Roulet (1986) found in the isolated ductus arteriosus of the guinea-pig that relaxation of tone occurred when intracellular pH was lowered by the ammonium chloride removal technique. However, it has long been known that the pulmonary artery constricts in response to hypoxia and acidosis, and intracellular acidification has been reported to constrict the vascular bed of the rabbit ear (Ighoroje and Spurway, 1984; Spurway and Wray, 1987). In tracheal smooth muscle from dog (Stephens and Mitchell, 1974) or rat (Twort and Cameron, 1986), contractility decreased as PCO_2 was raised and increased when PCO_2 was lowered. Stephens and Mitchell (1977) reasoned that an intracellular acidosis may be responsible for impairing contractility and demonstrated that hypercapnic strips were more acidic than those exposed to normocapnic conditions. It is of interest, however, that in this tissue intracellular pH became alkaline under hypoxic conditions, which was associated with a decrease of force (Stephens *et al.*, 1977). Little has been published on the influence of pH on intestinal contractions. Auberg *et al.* (1967) reported that extracellular acidosis relaxed the spontaneous contractions of isolated guinea-pig taenia coli, whereas Wienback *et al.* (1972) found that acidosis prolonged the period of spontaneous activity and concluded that contractility was raised.

The preceding discussion highlights various predicted and unexpected experimental observations, made predominantly on isolated animal models, and this may reflect true differences in various smooth muscle preparations, but more importantly may depend on the manner in which the acidosis is induced. If the extracellular acidosis is mediated by a diffusible acid, so that intracellular acidosis also occurs, an increase of force may occur. If the acidosis is confined to the extracellular space, the opposite or no effect may result. Fry and Liston (1989) reported in human and animal detrusor muscle that intracellular acidosis increased force, as in the experiments reported here, but extracellular acidosis depressed force, unlike the situation here where there was no effect. The reason for the diverse response to extracellular acidosis may be related to the dependence of detrusor muscle contraction on extracellular Ca^{2+} but the relative independence of extracellular Ca^{2+} for ureteric muscle contraction (Cole and Fry, unpublished data).

The mechanism for the positive inotropic action of intracellular acidosis is unclear. In cardiac muscle such a pH change depresses contractility (Fry and Poole-Wilson, 1981) and this has been ascribed to a reduction of the Ca^{2+} sensitivity of contractile proteins (Fabiato and Fabiato, 1978) as well as an attenuation of intracellular Ca^{2+} release and transmembrane currents. A report that acidosis can increase the Ca^{2+} sensitivity of the contractile proteins in vascular smooth muscle (Gardner and Diecke, 1988) could explain the above results, but the effect on ureteric muscle contractile proteins is unknown.

Implication of various ion-exchange mechanisms within the cell membrane could also explain the increase of force. A rise of intracellular $[H^+]$ may lead to a raised $[Na^+]$ via Na^+/H^+ exchange and this in turn may result in a raised intracellular $[Ca^{2+}]$ via a separate Na^+/Ca^{2+} exchange. Evidence from detrusor muscle might exclude this route since amiloride derivatives, which inhibit Na^+/H^+ exchange, do not inhibit the increase of force due to intracellular acidosis (Fry and Liston, 1989). However, other exchange mechanisms, such as Na^+-HCO_3^- co-transport, are insensitive to amiloride and would increase intracellular $[Na^+]$ during intracellular acidosis (Aickin, 1988). Measurement of intracellular Na^+ during intracellular acidosis will provide support for this potential mechanism.

A further mechanism by which acidosis could influence smooth muscle contraction is by means of local agents. Endothelial cells within the smooth muscle syncitium produce various factors such as prostaglandins which exert powerful effects on ureteric contractility (Cole *et al.*, 1988). The effect of intracellular and extracellular pH on the production of such agents is unclear at present but provides a possible modulatory function.

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The Authors

R. S. Cole, BSc, FRCS, Locum Director, Lithotripter Centre, St Thomas' Hospital

C H. Fry, BSc, BA, PhD, Senior Lecturer, Department of Physiology.

K. E D Shuttleworth, MS, FRCS, formerly Director, Lithotripter Centre.

Requests for reprints to R. S Cole, Lithotripter Centre, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH

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Immunofluorescent and Histochemical Staining Confirm the Identification of the Many Diseases Called Interstitial Cystitis

LARRIAN GILLESPIE, J. SAID, S. SOSTRIN and K. KLEIWER

Women's Clinic for Interstitial Cystitis, Beverly Hills, California, USA

Summary—Interstitial cystitis comprises a complex of diseases typified by symptoms of pelvic pain. Functional complaints do not aid the clinician in determining loss of anatomical capacity. Histochemical staining with PAS-colloidal iron/Van Geison's counterstain offers improved diagnostic ability for the pathologist and correlates well with immunofluorescent findings. Four distinct diseases can be identified through immunofluorescent staining, indicating that each is the result of different responses of the urothelium and endothelium to injury. Loss of bladder capacity associated with these diseases can be expected with age, but immunofluorescent staining for IgM within the capillaries of the interstitium is a more sensitive predictor.

The aetiology of interstitial cystitis has been as elusive as the ulcer which Hunner (1914), a gynaecologist at Johns Hopkins Hospital, first described. Numerous investigators have noted a similarity between systemic lupus erythematosus and interstitial cystitis (Fister, 1938; Silk, 1970; Jokinen *et al.*, 1972; Rodriguez-du la Serna and Alarcon-Segovia, 1981, Weisman *et al.*, 1981) as well as ulcerative colitis (Bohne *et al.*, 1962; Rebuck *et al.*, 1962; Boye *et al.*, 1972). Jokinen *et al.* (1972) and felt that interstitial cystitis belonged to a group of autoimmune diseases in which the disease is restricted to one organ but the autoantibodies are non-organ specific. In contrast, Smith and Auerbach (1952) expressed their suspicion that "interstitial cystitis may represent the end stage in a bladder that has been made irritable by emotional disturbance."

While the diagnosis of interstitial cystitis has been the subject of spirited debate in the world literature, no universal criteria have been accepted which would allow for intercontinental comparisons of treatment. The use of mast cell counts has been championed by the Scandinavian countries (Larsen *et al.*, 1982; Fall *et al.*, 1987); reduced anatomical bladder capacity has been favoured by the British Isles (Turner-Warwick and Handley Ashken, 1967; Kirby and Turner-Warwick, 1986), while the United States has popularised the appearance of petechial haemorrhages with or without loss of anatomical capacity (Messing and Stamey, 1978). These incongruities, however, may mean that interstitial cystitis is not one disease but several, which need to be differentiated along comparative lines.

The purpose of this study was 4-fold: (1) to examine the diagnostic parameters by which one should clinically suspect the many diseases called interstitial cystitis and to determine if functional complaints correlated with reduced capacity; (2) to determine if those patients with the identical symptom complex but normal bladder capacity represented an earlier or evolving stage of these diseases rather than different entities; (3) to establish new urohistological and immunofluorescent criteria for the identification of these different disease processes; (4) to assess the impact of age on bladder capacity of those patients with interstitial cystitis and its association with immunofluorescent staining patterns.

Patients and Methods

A total of 339 patients (334 female, 5 male) were referred from throughout the continental United

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States with symptoms of pelvic pain in the face of repeated sterile urine cultures. They ranged in age from 16 to 76 years. They were questioned with regard to menstrual irregularities, bowel problems, fevers, malaise, joint pains or rashes, in addition to symptoms of pressure, frequency/urgency, nocturia and burning before or after voiding. Patients with positive urine cultures associated with symptoms during this period were excluded from the study. Patients with positive bacterial, fungal or chlamydial vaginal or prostatic fluid cultures were treated and then re-evaluated for persistence of symptoms in the absence of these infections; 238 patients had been diagnosed as suffering from trigonitis, urethritis, abacterial prostatitis or hypersensitive bladder syndrome.

Repeat urine analysis and culture were obtained 1 h before performing cystoscopy with hydrodilatation under general anaesthesia. The bladder was filled passively with sterile water at 70 mm pressure to determine anatomical capacity. The appearance or absence of a haemorrhagic effluent was noted. Repeat cystoscopy was performed to evaluate the appearance of petechial haemorrhages, ulcerations, linear striations or fissures. Cold cup pinch biopsies were taken from these sites and, if possible, from "normal" or non-haemorrhagic areas of the bladder for comparison. Specimens obtained at surgery were placed in Bouin's solution for histological evaluation and Zeus medium for immunofluorescent studies (Zeus fixative, Zeus Scientific, Raritan, USA). A double-blind study was performed by having all specimens evaluated by 2 independent pathologists with no knowledge of either the patients or each other's findings. Control tissue biopsies were obtained from 5 female volunteers from the nursing staff who denied symptoms of irritation, frequency, pressure or burning. Two of the volunteers had a history of at least 1 urinary tract bacterial infection.

PAS staining with a colloidal iron-Van Geison's counterstain was done on Bouin's fixed specimens in order to assess the acid mucopolysaccharide content of the urothelium. This technique results in a colour-coding which stains non-acid mucopolysaccharides pink, acid mucopolysaccharides blue and protein brown.

Immunofluorescent staining was performed on Zeus fixed specimens in the following manner. After 1 to 4 h, tissue blocks were washed in citrate buffer and snap frozen in isopentane and dry ice at −60° C. Cryostat sections were cut at 4 to 6 μm and fixed for 5 min in cold acetone. Slides were washed for 30 min in phosphate buffered saline (PBS) at pH 7.4 and incubated for 30 min with fluorescein conjugated rabbit anti-human IgG, IgA, IgM and IgE (heavy chain specific), C3 and fibrinogen (DAKO Corporation, Santa Barbara, USA). Slides were then washed in PBS and examined with a Zeiss fluorescent microscope using vertical illumination. In 11 cases biopsies obtained under identical conditions were frozen immediately after surgery and stained in parallel with Zeus fixed biopsies as described above. No difference in staining patterns was observed between these 2 groups.

Results

Table 1 shows the distribution of symptoms in the 339 patients who were studied for a painful pelvis syndrome. Patients were divided into 2 groups: those in Group 1 were found to have anatomical bladder capacities $\leqslant 400$ ml and Group 2 was composed of patients with capacities >400 ml. Frequency/urgency was the most common symptom in both groups. Nocturia, pressure and burning before or after voiding were variable. Menstrual irregularities were infrequently reported. The incidence of systemic disease symptoms was also noted. There was no significance in the distribution of symptoms between the 2 groups, indicating that functional complaints do not aid the clinician in predicting anatomical capacity.

Endoscopic findings

Table 2 summarises the cystoscopic findings. Haemorrhagic effluent was noted in only 214 patients. Petechial haemorrhaging was reported in 311 patients, with distinct visible ulceration in 78. Increased capillary growth, or angiogenesis, however, was noted in 329 cases, serving as the most reliable endoscopic criterion for identification of this symptom complex regardless of bladder capacity. Petechial haemorrhaging and angiogenesis were the most frequent endoscopic findings in patients with bladder capacities >400 ml, while ulceration (Hunner's ulcers) was seen in 88.4% of patients with bladder capacities $\leqslant 400$ ml. Reliance upon the identification of ulcerations was the poorest predictor of interstitial cystitis (23%). None of the controls demonstrated any changes in cystoscopic appearance with hydrodilatation.

Figure 1 demonstrates the variable endoscopic appearances of the many diseases called interstitial cystitis. Increased angiogenesis, in particular the appearance of tortuous, spiral vessels, can be noted prior to distension. After hydrodilatation and

Table 1 Symptoms in 339 Patients with Pelvic Pain

	Bladder capacity	
	Group 1 *<400 ml* *(n=104)* *(%)*	*Group 2* *>400 ml* *(n=235)* *(%)*
Frequency/urgency	104 (100)	205 (87)
Nocturia	103 (99)	198 (84)
Burning	83 (79)	174 (74)
Pressure	91 (87)	152 (64)
History of urinary tract infection	82 (78)	213 (98)
Joint pains	54 (52)	114 (48)
Bowel cramps	38 (36)	79 (33)
Rashes	12 (11)	38 (16)
Fever	42 (40)	91 (38)
Menstrual problems	12 (38)	51 (21)

Table 2 Endoscopic Findings in Patients with Pelvic Pain

	Bladder capacity	
	Group 1 *<400 ml* *(n=104)* *(%)*	*Group 2* *>400 ml* *(n=235)* *(%)*
Haemorrhagic effluent	98 (94)	106 (45)
Petechial haemorrhages	101 (97)	210 (89)
Ulceration/fissures	69 (66)	9 (3)
Angiogenesis	103 (99)	226 (96)

decompression, petechial haemorrhaging can be seen arising from capillary branches, while linear striation was observed to follow the arterioles. Ulcerations, fissures and flame haemorrhages were noted as above.

Histological findings

PAS stains with colloidal iron-Van Geison's counterstains were developed to assess the absence or presence of a mucous layer, the acid mucopolysaccharide content of the transitional epithelium, and to aid in the identification of proteinaceous material. Figure 2A demonstrates normal tissue in which the mucous layer is present in over 90% of the specimen. The acid mucopolysaccharide content is homogeneous throughout the urothelium and there is minimal haemorrhage from the biopsy in the interstitium. No proteinaceous material is noted either on the urothelium or in the interstitium. Figure 2B exemplifies the dramatic changes seen with interstitial cystitis. The mucous layer is greatly decreased or absent while the epithelium shows cellular loss of integrity with resultant ulceration. The acid mucopolysaccharide content of the epithelium is greatly reduced. There is a proteinaceous infiltrate within the urothelium and throughout the interstitium. Marked oedema together with angiectasia and haemorrhage can be seen in the interstitium. These characteristic findings were consistent in both groups of patients and did not correlate either with the severity of symptoms or with loss of bladder capacity. Haematoxylin and eosin stains merely showed interstitial oedema and angiectasia in both groups. Neither carcinoma nor tuberculosis was found in any of the 339 patients.

Immunofluorescent findings

Immunofluorescent staining was used to evaluate 678 tissue specimens (339 patients), in addition to specimens from 5 normal volunteers. Control bladder biopsies from the 5 asymptomatic volunteers were negative for immunoglobulin, complement and fibrinogen, with the exception of 1 case which revealed rare IgA positive cells at the urothelial surface. Antigenic staining for fibrinogen within the lamina propria or throughout the interstitium was noted in 662 specimens, serving as a reliable indicator for this disease complex. Eight patients (16 specimens) were negative for immunoglobulins, complement and fibrinogen, and were therefore excluded from having interstitial cystitis.

The immunofluorescent staining patterns observed in the remaining 331 patients fell into 4 distinct categories: Group 1: IgA and fibrinogen; Group 2: IgM and fibrinogen; Group 3: IgA, IgM and fibrinogen; Group 4: fibrinogen only. Staining for C3 and IgG did not occur alone but was noted in association with vascular IgM staining with fibrinogen in 53 specimens (not shown in Table 3). IgE was only seen in addition with mast cells in 5 specimens. Positive antigenic staining for IgA was noted in 70 patients, predominantly within the cytoplasm of surface urothelial cells, in some cases involving all layers of the urothelium to the basement membrane. Staining for IgA was noted only on the surface of the urothelium in 19 patients who had positive urine cultures at the time of the biopsy. Antigenic staining for IgM was noted within either the small vessel walls or the epithelium in 67 cases, while staining for IgA within the urothelial cytoplasm was associated with positive staining for IgM within the capillaries in 85 patients. Staining for fibrinogen alone was present within subepithelial connective tissue in 109 cases.

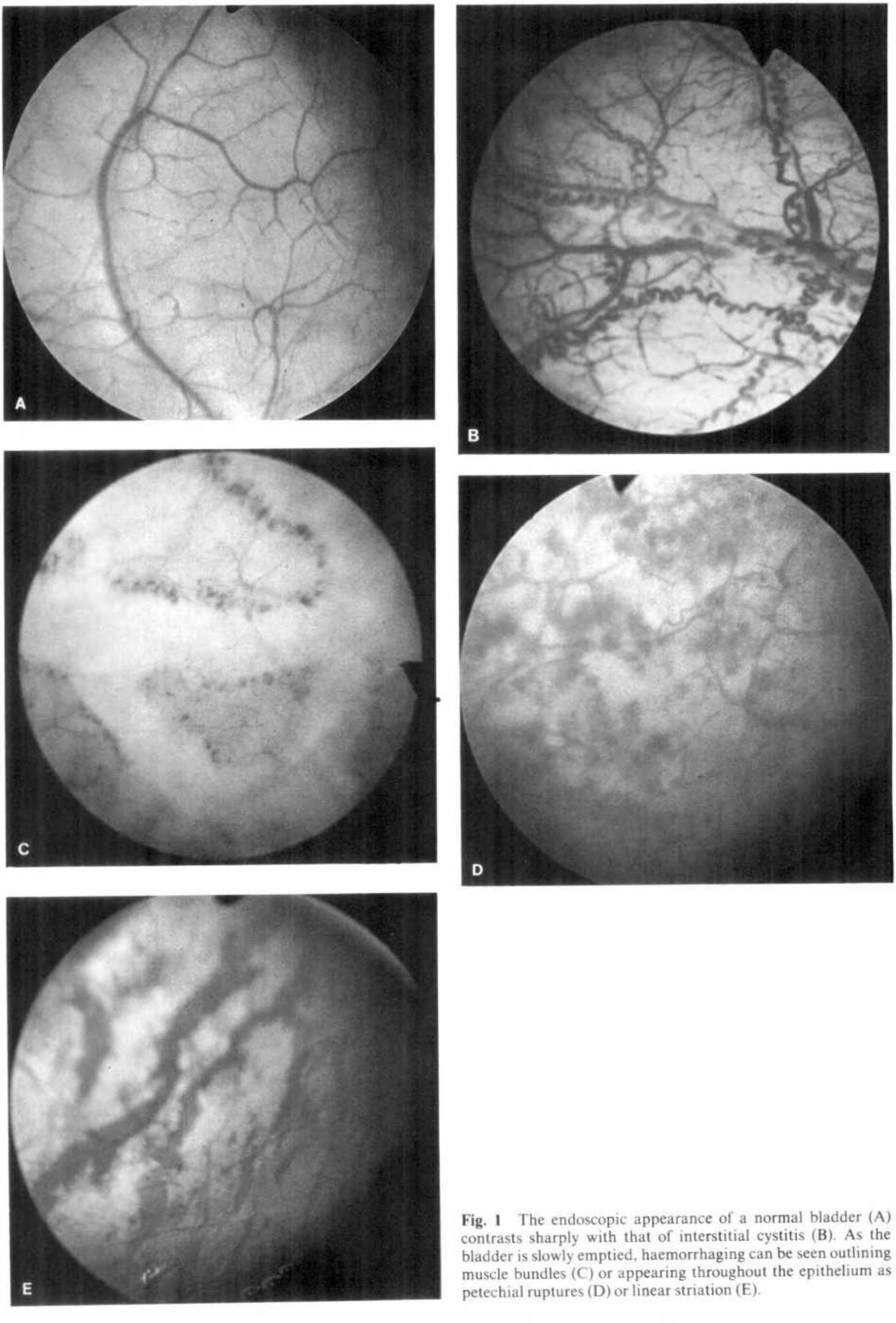

Fig. 1 The endoscopic appearance of a normal bladder (A) contrasts sharply with that of interstitial cystitis (B). As the bladder is slowly emptied, haemorrhaging can be seen outlining muscle bundles (C) or appearing throughout the epithelium as petechial ruptures (D) or linear striation (E).

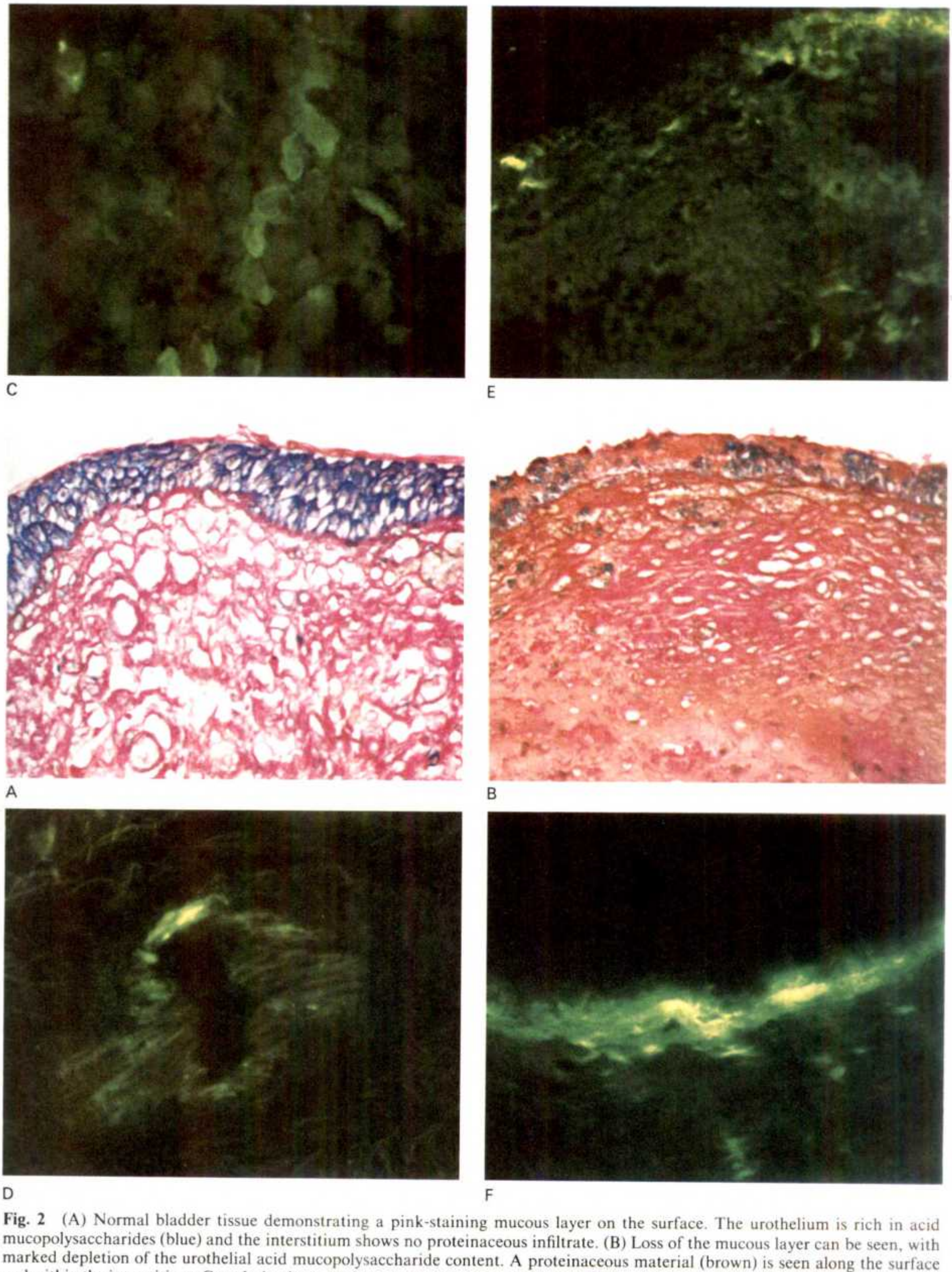

Fig. 2 (A) Normal bladder tissue demonstrating a pink-staining mucous layer on the surface. The urothelium is rich in acid mucopolysaccharides (blue) and the interstitium shows no proteinaceous infiltrate. (B) Loss of the mucous layer can be seen, with marked depletion of the urothelial acid mucopolysaccharide content. A proteinaceous material (brown) is seen along the surface and within the interstitium. Correlation between immunofluorescent staining and the van Gieson's colloidal iron stain demonstrates secretory IgA (C) within the epithelium, IgM (D) within the endothelium of interstitial capillaries, and staining for fibrinogen (E) within the interstitium or (F) along the lamina propria

Table 3A illustrates the association between bladder capacity and immunofluorescent staining, indicating that loss of anatomical capacity was associated most frequently with patients in Group 3 (41.8%). If we take Groups 2 and 3 together (Table 3B), assuming that staining for IgM is the critical factor, then this association increases to 67.65%, while not affecting the lack of association with normal capacity.

Table 4 examines the findings of decreased bladder capacity and age; 79% of patients with positive antigenic staining for the many diseases called interstitial cystitis will be less than 50 years of age if their bladder capacity exceeds 400 ml, but 57.69% of patients with a capacity ≤400 ml will be over 50 years of age ($P=0.0001$). The correlation coefficient between age and bladder capacity was -0.21, indicating that as age increases alone, loss of bladder capacity with these diseased entities can be expected.

Table 3A Immunofluorescent Staining and Bladder Capacity

	Bladder capacity		
	Group 1 <400 ml (n=102) (%)	*Group 2 >400 ml (n=229) (%)*	*Total*
Negative	2	6	0
Group 1 (IgA+Fibrinogen			
Frequency	12	58	70
Percent %	3.63	17 52	21.15
Row %	17.14	82.86	
Column %	11.76	25 33	
Group 2 (IgM+Fibrinogen)			
Frequency %	27	40	
Percent %	8.16	12 08	67
Row %	40 30	59.70	20 24
Column %	26 47	17.47	
Group 3 (IgA, IgM+Fibrinogen)			
Frequency	42	43	
Percent %	12 69	12 99	85
Row %	49 41	50 59	25.68
Column %	41.18	18 78	
Group 4 (Fibrinogen only)			
Frequency	21	88	
Percent %	6.34	26.59	109
Row %	19.27	80.73	32 93
Column %	20.59	38.43	
Total	102	229	331
	30.82	69.18	100.00

29.571, DF=3, $P=0.0001$.

Table 3B Immunofluorescent Staining and Bladder Capacity

	Bladder capacity		
	<400 ml	*>400 ml*	*Total*
IgM+Fibrinogen			
Frequency	69	83	152
Percent %	20.85	25.07	45.92
Row %	45.39	54 61	
Column %	67.65	36 25	

Table 4 Bladder Capacity and Age

Bladder capacity	*<50*	*>50*	*Total*
≤400 ml			
Frequency	44	60	104
Percent %	12.98	17.70	30.68
Row %	42.31	57.69	
Column %	20.47	48.39	
>400 ml			
Frequency	171	64	235
Percent %	50.44	18 88	69.32
Row %	72.77	27.23	
Column %	79.53	51 61	
Total	215	124	339
	63.42	51 61	100.00

χ^2 28 830, DF=1, $P=0$ 0001

Table 5 demonstrates the association between age and bladder capacity and the immunofluorescent group stainings. If the patient has a capacity >400 ml, antigenic staining for fibrinogen only was most often found regardless of age. However, if capacity was ≤400 ml, staining for Group 3 was seen most often if the patient was over 50 years of age. If we look at the association between bladder capacity as predicted by immunofluorescent categories, 89% of patients who demonstrated antigenic staining for IgM within the capillaries were found to have a capacity <400 ml under anaesthesia.

Correlation between immunofluorescence and urohistochemical staining

Figures 2C–F demonstrate the comparison between findings of proteinaceous material on urohistochemical staining and immunofluorescent results. IgA was found to correlate with the appearance of protein within the urothelium, while IgM agreed favourably with the appearance of increased angiectasia within the interstitium. Staining for fibrinogen was consistent with the proteinaceous infiltrate seen either along the lamina propria or within the interstitium. All findings were reported in a double-blind fashion by 2 independent pathologists, confirming that the PAS-colloidal iron/Van Geison's counterstain offers a histopathologist

Table 5 Age and Bladder Capacity in Relation to Immunofluorescent Staining

Bladder capacity	*None*	*Group 1* *IgA+Fib*	*Group 2* *IgM+Fib*	*Group 3* *IgA, IgM+Fib*	*Group 4* *Fib*	*Total*
<400 ml (age <50 years)						
Frequency	1	4	16	12	11	43
Percent %		1.21	4.83	3.63	3.32	12.99
Row %		9.30	37.21	27.91	25.58	
Column %		5.71	23.88	14.12	10.09	
<400 ml (Age >50 years)						
Frequency	1	8	11	30	10	59
Percent %		2.42	3.32	9.06	3.02	17.82
Row %		13.56	18.64	50.85	16.95	
Column %		11.43	16.42	35.29	9.17	
>400 ml (Age <50 years)						
Frequency	6	40	33	29	63	165
Percent %		12.08	9.97	8.76	19.03	49.85
Row %		24.24	20.00	17.58	38.18	
Column %		57.14	49.25	34.12	57.80	
>400 ml (Age >50 years)						
Frequency	0	18	7	14	25	64
Percent %		5.44	2.11	4.23	7.55	19.34
Row %		28.13	10.94	21.88	39.06	
Column %		25.71	10.45	16.47	22.94	
Total		70	67	85	109	331
		21.15	20.24	25.68	32.93	100.00

χ^2 42.222, DF=9, P=0.0001

improved diagnostic ability in distinguishing the many diseases called interstitial cystitis.

Discussion

The presence of a sterile urine culture has resulted in an unsatisfactory response to antibiotic therapy and even hysterectomy or prostatectomy in patients with chronic pelvic pain, frustrating many practitioners in their attempts to differentiate reproductive organ disease from urological dysfunction. Functional complaints have been shown in this study not to correlate with anatomical capacity, suggesting that another mechanism, such as an incompetent urothelial membrane, may allow the contents of urine to interact with receptor mechanisms, producing symptoms of either burning, pressure/cramp or frequency. The demonstration urohistologically of the acid mucopolysaccharide content in normal tissue, and its loss in diseased tissue, supports the theory that an environmental barrier exists in normal tissue which prevents the contents of urine from interacting with the free radicals and toxins in urine (Parsons *et al.*, 1980).

Techniques used for immunofluorescent microscopy in this study are adaptations of standard methods used to study kidney and skin biopsies. The use of snap frozen tissue for preservation of antigens is essential and results cannot be extrapolated to studies on fixed tissue with other techniques such as immunoperoxidase. Zeus fixative was used for convenient transport of specimens to the laboratory. Controls using fixed and unfixed specimens revealed that this did not alter staining patterns (Said *et al.*, 1989), as has been demonstrated in studies on renal (Fliegel *et al.*, 1983) and lymphoid tissue (Palutke *et al.*, 1986).

The present study does not support the hypothesis that there are 2 kinds of interstitial cystitis (Fall *et al.*, 1987) but rather that separate, distinct entities can be identified through immunofluorescent characteristics which are the result of unique changes to the gel phase of the bladder interstitium. This technique offers a common language by which one can categorise these diseases and therefore select therapy aimed at controlling specific tissue responses to damage. We propose that Group 1 (IgA and fibrinogen) represents an inflammatory, not immune-mediated response to tissue injury which results in loss of urothelial membrane integrity. Localised therapy, which is instilled in the bladder, should be effective in stimulating membrane regeneration (Gillespie *et al.*, 1985). Group 2 (IgM and fibrinogen) represents vascular endothelial injury which is systemic in nature and would therefore require systemic therapy to control tissue response (Gillespie, 1988). Group 3 (IgA, IgM and fibrinogen) contains both inflammatory and immune-mediated responses and would require both local and systemic therapy. Finally, the presence of fibrinogen alone (Group 4) would indicate a cellular or humoral response and should be investigated for hormonal, viral, environmental and mechanical factors (Gillespie and Jones, 1986).

The appearance of increased capillary growth, or angiogenesis, offers another sensitive indicator for the clinician of an interstitial response to cellular injury. Angiogenesis, the formation of new blood vessels, can be the result of both inflammatory and immune-mediated responses, induced by the leakage of fibrinogen from post-capillary venules (Senger *et al.*, 1983). The fibrin gel that subsequently forms in the extravascular space appears to play an important role in the build-up of a new capillary bed (Dvorak, 1986). Antigenic staining for fibrinogen within the interstitium supports this hypothesis.

The unique correlation between the urohistochemical stain and immunofluorescence offers a broader and more complete pathological identification of the urothelial tissue response in the many angiogenic diseases called interstitial cystitis. Other syndromes, such as trigonitis, urethritis, abacterial prostatitis and hypersensitive bladders should be routinely evaluated by these techniques, since many, though not all, are the result of similar urothelial injuries (Witherow *et al.*, 1989).

Finally, this study invalidates the concept that interstitial cystitis is *de facto* a disease of postmenopausal females. Although loss of bladder capacity from this disease process with increasing maturity can be expected, the presence of antigenic staining for IgM within the capillaries is a greater predictor of decreased capacity than age. It is also interesting to note that Monson *et al.* (1988) demonstrated rupture to the lamina in rabbit bladders merely with overdistension. Perhaps this explains the inclusion of patients with detrusor myopathy in these disease entities. Clinical diagnosis of this disease process by anatomical capacity may account for the great disparity of opinion as to its incidence in the general populace (Kinder *et al.*, 1958; Garrelts, 1966). Recognition that interstitial cystitis is not one disease, but many, which result from different environmental and metabolic factors funnelling into a common pathway, will result in earlier, confident diagnosis of these "painful bladder syndromes" and the development of therapy aimed at their arrest.

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The Authors

Larrian Gillespie, MD, Clinical Instructor, Urology, University of California at Irvine, Director of the Women's Clinic for Interstitial Cystitis, Beverly Hills, California

J Said, MD, Associate Pathologist, Cedars-Sinai Medical Center, Los Angeles, Associate Clinical Professor, Pathology, University of California at Los Angeles

S Sostrin, MD, Associate Clinical Professor, Pathology, University of Southern California

K Kliewer, MD, Assistant Clinical Professor, Pathology, University of California at Los Angeles

Request for reprints to Larrian Gillespie, The Women's Clinic for Interstitial Cystitis, 120 S Spalding Dr #210, Beverly Hills, California 90212, USA

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Do Women with Idiopathic Sensory Urgency have Early Interstitial Cystitis?

M I. FRAZER, B. T. HAYLEN and M. SISSONS

University Department of Obstetrics and Gynaecology, and University Department of Pathology, Royal Liverpool Hospital, Liverpool

Summary—Interstitial cystitis is rarely considered as a cause of urinary symptoms in referrals to gynaecology clinics. Recent concepts in the diagnosis of this condition mean that it is emerging as a much more common entity, with both early and late forms of the disease being described. Mast cell density in the detrusor muscle has been reported to be useful as a disease marker to substantiate the diagnosis of interstitial cystitis where no classical diagnostic features exist. We assessed mast cell counts in bladder biopsies from 27 women with idiopathic sensory urgency and 10 control patients about to undergo a colposuspension procedure for pure genuine stress incontinence; 30% of the study group had a clear increase in the detrusor muscle mast cell population (detrusor mastocytosis). No control patient showed such an increase Early interstitial cystitis should be considered as a possible cause of lower urinary tract symptoms in patients with apparently idiopathic sensory urgency.

Interstitial cystitis may be unfamiliar to gynaecologists as a possible cause of urinary symptoms in gynaecological referrals. The disorder is traditionally thought of as a painful and debilitating ulcerative pancystitis, occurring predominantly in females, resistant to therapy and of obscure aetiology. On this basis the diagnosis is not difficult (although uncommon) and patients usually present to a department of urology rather than gynaecology.

Recently, however, it has become common practice to divide interstitial cystitis into 2 grades of severity: the so-called "classical disease" with florid cystoscopic changes such as ulceration on distension (Hunner, 1915) and an "early" or "non-ulcerative" form. This latter entity may show abnormalities (such as petechial haemorrhages in the urothelium) only after refill cystoscopy (Messing and Stamey, 1978; Fowler, 1981; Fall *et al.*, 1986). Patients with early interstitial cystitis are of great interest to gynaecologists because they may present similarly to women with symptoms of urinary frequency and urgency without obvious cause (idiopathic sensory urgency). These latter patients often present to a department of gynaecology, particularly one with an interest in uro-gynaecology. The lack of objective abnormality and the moderate success of some psychological retraining methods have led to the belief that these are primarily psychogenic disorders (Hafner *et al.*, 1977, Macaulay *et al.*, 1987). Any attempt at a pathological comparison between early interstitial cystitis and idiopathic sensory urgency requires the use of an objective criterion. Until recently such a criterion was not available, since there appeared to be no single histological feature which would lead to a definitive diagnosis of interstitial cystitis (Bowen *et al.*, 1986).

Early interstitial cystitis and mast cells

Mast cell density is known to be increased in the bladder walls of patients with interstitial cystitis (Bohne *et al.*, 1962) Despite this, it was not until comparatively recently that the first attempt was made to quantify mast cells in bladder biopsy specimens from patients with established and suspected early disease (Larsen *et al.*, 1982). It was found that mast cell counts within the detrusor muscle could distinguish between (1) patients with

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“classical” disease diagnosed cystoscopically, (2) patients with suggestive symptoms but normal cystoscopy, and (3) normal individuals. Messing and Stamey (1978) studied qualitative assessments of mast cell density retrospectively and concluded that such assessments produced no diagnostically useful information. A wide range of fixing and staining techniques is used to identify mast cells in tissues. Mast cells are notoriously elusive without the use of special procedures and much of the reported differences in the literature may be accounted for by these factors alone.

Later work has continued to suggest that in early disease, mast cell counts within the detrusor muscle can be used both as a reliable disease marker and also to substantiate the diagnosis of interstitial cystitis in uncertain cases (Feltis *et al.*, 1987). Patients with a suggestive history and detrusor mast cell counts $\geqslant 28/\text{mm}^2$ of muscle are considered to have detrusor mastocytosis and, by inference, interstitial cystitis (Larsen *et al.*, 1982). Despite this substantial body of opinion in favour of the usefulness of quantifying mast cells, particularly in the detrusor muscle, this is an area of great controversy in urological practice and doubts remain on the role of the mast cell (Bowen *et al.*, 1986, Holm-Bentzen *et al.*, 1987, Messing, 1987, Anderson *et al.*, 1989).

With this background we believed it would be interesting to study mast cell counts in biopsy specimens from women attending a gynaecological urodynamic clinic who were diagnosed as suffering from idiopathic sensory urgency, to see if a diagnosis of early interstitial cystitis, as defined by the presence of detrusor mastocytosis, could be substantiated.

Patients and Methods

Patients were recruited from referrals to the Professorial Urodynamic Clinic at the Royal Liverpool Hospital. All presented with disabling symptoms of urinary urgency and frequency (more than 7 voids/day) as objectively demonstrated on 7-day frequency and volume charts. Symptoms had been present for at least 6 months. No patient had bladder pain as a specific presenting feature, although some complained of pain on filling cystometry (see below).

Following a full history and examination, urodynamic testing was performed which included sitting, provocative cystometry and urethral pressure measurements at rest and during stress. All definitions and units conform to standards proposed by the International Continence Society unless otherwise stated.

Patients were included in the study if urodynamic testing revealed a stable bladder, if the maximum cystometric bladder capacity was $\leqslant 400$ ml, with or without pain, or 500 ml if pain was felt on filling cystometry, if a clean catch midstream specimen of urine was uninfected and apyuric, and if subsequent cystoscopy was normal. The urodynamic criteria were deliberately open and relatively unrestricted.

Twenty-seven patients were selected and underwent bladder biopsy at the time of the initial cystoscopy. They represented 10.4% of the urodynamic referral population over the time period of the study. This percentage of sensory urgency accords well with percentages reported by other gynaecological urodynamic clinics (Hilton, personal communication) and our group thus appeared representative of patients attending similar clinics elsewhere. Cystoscopy was carried out by the same observer during and after filling the bladder for 1 min at a pressure of 80 cm of water (Messing and Stamey, 1978). The mucosa was examined for erythema and ulceration on filling, as well as the presence of petechial haemorrhages after decompression and subsequent refill examination. Total bladder capacity was noted under the anaesthetic.

Three bladder biopsy specimens were obtained with punch biopsy forceps from the dome, right and left lateral walls of the bladder. Control biopsy samples of the bladder wall were obtained from 10 patients undergoing a Burch colposuspension procedure. Controls and subjects were well matched for age and parity. All gave informed consent and the study was approved by the local ethical committee.

Two of the biopsies were fixed in Carnoy's solution and stained for the counting of mast cells using naphthol ASD chloroacetate (Leder, 1964). This particular staining and fixing method was found to give better results than other methods in a comparative study by Frazer (1988). The third specimen was stained using haematoxylin and eosin and sent for routine histology to exclude carcinoma *in situ* (Smith and Badenoch, 1965). Fibrosis, inflammation and oedema were also assessed in these sections by a pathologist (M.S.) who was unaware of the mast cell counts.

Counting mast cells

Mast cells were counted in the mucosa/lamina propria and within the detrusor muscle bundles by a single observer (M.I.F.). This technique was found to be highly reproducible in a preliminary study of the characteristics of mast cells staining in human ileum (Frazer, 1988). Two biopsies from each patient were evaluated in this way using a calibrated graticule at ×400 magnification. Since mature mast cells may be as much as 25 µm in diameter, slide material was chosen in a non-serial fashion with slides to be counted each separated by 4 intervening sections. Only those mast cells within muscle bundles (intrafascicular) were counted (Larsen *et al.*, 1982). Mast cells associated with vascular tissue or in the surrounding areolar tissue were not included as being in the detrusor proper. Each mean mast cell count was based on a minimum of 20 high power field counts.

Statistics

Non-parametric statistics (Wilcoxon's rank sum and Fisher's exact probability tests) were used on the mast cell and clinical data.

Results

The clinical characteristics of the study group are summarised in Table 1. Table 2 summarises the urodynamic and cystoscopic data.

Of the 27 patients included in the study, 6 (22%) showed petechial haemorrhages on refill cystoscopy. None showed the classical signs of interstitial cystitis or any evidence of a contracted bladder under general anaesthesia.

Mucosal/lamina propria mast cells

In subjects and control specimens, mast cells were frequently observed in the mucosa and lamina propria (Fig. 1). Many of these cells were associated with the vascular supply and so their numbers tended to vary according to the vascularity of the region included in the plane of section. The mean number of mast cells in hypersensitive bladders was 64/mm^2 (range 0–125) and in control material 48/mm^2 (range 0–124). This difference was not significant as assessed by the Wilcoxon rank sum test.

Table 1 Clinical Characteristics of Patients with and without Detrusor Mastocytosis

	Controls (n=10)	*Without mastocytosis (n=19)*	*With mastocytosis (n=8)*
Mean age (years)	43.3	47.6	47.4
	(35–58)	(21–65)	(31–60)
Mean parity	2.5	1.8	2.3
Smoker (>10/day)	5 (50%)	8 (42%)*	1 (13%)*
Total abdominal hysterectomy/vaginal repair	4 (40%)	5 (26%)	3 (38%)
Duration of symptoms (months)		44.7†	63.9†
		(6–120)	(10–120)

* Not significant. Fisher's exact probability test $P=0.297$

† Not significant. Wilcoxon's rank sum test

Table 2 Cystoscopic and Urodynamic Findings in 27 Patients with Idiopathic Sensory Urgency

	Without mastocytosis	*With mastocytosis*
No. of patients	19	8
Cystoscopy findings		
Petechiae	5 (26%)	1 (13%)
Bladder capacity (ml, under G.A.)	694	631
(means and range)	(380–1000)	(450–900)
Urodynamic data		
First sensation (ml)	110	184
(means and ranges)	(20–195)	(50–300)
Cystometric bladder Capacity (ml)	370	386
(means and range)	(50–500)	(278–500)
Pain on filling	3 (16%)*	4 (50%)*

* Not significant. Fisher's exact probability test $P=0.39$

Detrusor muscle mast cells

In both subjects and controls (Fig. 2) there was a subgroup in which either there were no mast cells or they were so infrequent as to make a valid count impossible (13/27 (48%) subjects; 7/10 (70%) controls). Where mast cells could be counted there was a group of 8 women (30%) with idiopathic hypersensitivity who had detrusor mastocytosis (Larsen *et al.*, 1982), *i.e.* a count >28 mast cells/mm^2 of detrusor muscle. No control subject had detrusor mastocytosis.

Histology

Only 2 patients showed mild fibrosis and inflammatory changes greater than those found in the control biopsy specimens. Both patients had detrusor mastocytosis. No patient had changes sufficient to classify her as having interstitial cystitis on light microscopy alone.

Discussion

In patients presenting to a department of gynaecology there is a subgroup of women with apparently idiopathic hypersensitivity who have detrusor mastocytosis and therefore may be suffering from a form of interstitial cystitis. This subgroup com-

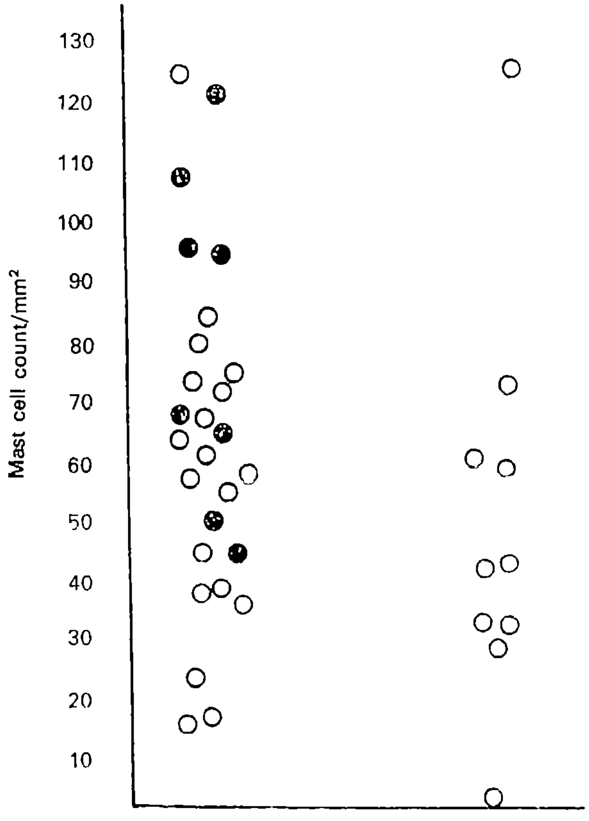

Fig. 1 Mucosal/lamina propria mast cells in subjects and controls ● = patients with detrusor mastocytosis

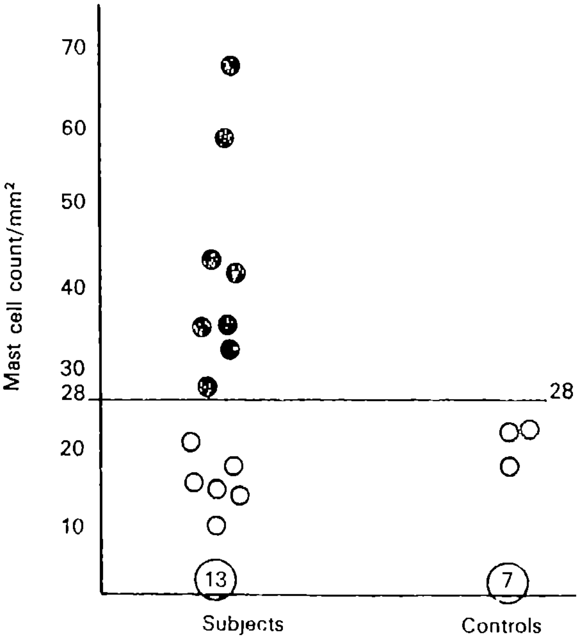

Fig. 2 Detrusor mast cell counts in subjects and controls ● — mastocytosis The number in the circle refers to the number of patients in each group who had no mast cells in the detrusor

prised 30% of the 27 patients in the present trial and represented 3% of new referrals.

There were no marked clinical differences between women with mastocytosis and those without Age, duration of symptoms, parity or a history of pelvic surgery offered no clues as to the aetiology of mastocytosis and there were no differences in urodynamic or cystoscopic findings The presence of petechial haemorrhages on refill distension did not predict which patients were likely to have mastocytosis. The current emphasis on this cystoscopic aspect in the diagnosis of early interstitial cystitis may be misleading Mucosal petechiae have been noted in patients without symptoms (Fall *et al.*, 1986). Small areas of subendothelial bleeding are probably a general response of the urothelium to acute trauma. They do not appear to be specific enough to make a diagnosis in any individual patient without careful examination of an adequate biopsy.

These findings agree with those of earlier workers studying women with "painful bladder disease" (Feltis *et al*, 1987), but disagree with others (Fall *et al*, 1987), where marked clinical differences were found between patients with and without mastocytosis

It is unlikely that the detrusor mastocytosis which we observed is a primary phenomenon The proliferation of mast cells is probably the result of unknown stimuli acting within the bladder wall Mast cells contain many potent physiologically active substances which can be released into the tissues on cell degranulation, including kallikrein, a proteolytic hormone which produces bradykinin from inactive kininogen Bradykinin is known to produce discharge of mechanosensitive sensory endings in the bladder (Floyd *et al*, 1977) and the alteration of these receptors by bradykinin provides a tentative explanation of the genesis of symptoms in these patients. It also opens up novel avenues of thought regarding the aetiology and treatment of symptoms in this subgroup. One speculation is that abnormalities of the protective mucin layer of the transitional epithelium, either qualitative or quantitative, may allow access of harmful urinary constituents into the deeper layers of the bladder wall. This may act as the primary sensitising mechanism of mast cell proliferation. Evidence for the existence of such abnormalities in interstitial cystitis has emerged in recent years (Parsons, 1987).

Consideration should be given to the possibility that early interstitial cystitis is the cause of lower urinary tract symptoms in patients with sensory urgency who present without bladder pain. The quantification of mast cells in bladder biopsies from women with apparently idiopathic hypersensitivity divides them into 2 groups; those with and those without detrusor mastocytosis. This appears to be a useful distinction based on objective histopathological differences and cannot be made on clinical criteria alone The long-term prognosis in patients with idiopathic sensory urgency is unclear. In particular, it is not yet known whether patients with detrusor mastocytosis go on to develop signs of classical interstitial cystitis. Longitudinal studies should answer this question. It would be particularly interesting to compare the long-term outcome of patients with and without detrusor mastocytosis.

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The Authors

M I Frazer, MD, MRCOG, First Assistant University Department of Obstetrics and Gynaecology, Newcastle General Hospital, Newcastle upon Tyne

B T Haylen, MD, MRCOG, FRACOG, Specialist Obstetrician and Gynaecologist, St Margaret's Hospital, Sydney, Australia

M Sissons, MD, MRCPath, Consultant Pathologist, Blackpool General Hospital, Blackpool

Requests for reprints to M I Frazer, Department of Obstetrics and Gynaecology, Gold Coast Hospital, Nerang Street, Southport 4215, Queensland, Australia

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Assessment of Residual Urine in Men Following Catheterisation

S. F. PURKISS

Department of Surgery, Princess Margaret Hospital, Swindon

Summary—There is a certain volume of urine left within the bladder which cannot be drained by a catheter. A dilutional method was used to calculate this residual volume in 15 men, 10 had acute retention secondary to benign prostatic hyperplasia and 5 had permanent indwelling catheters for neurogenic urinary incontinence.

The mean catheterised residual volume was 98.53 ml for patients with acute retention and 14.48 ml for patients with long-term catheters.

The explanation for higher post-catheterisation volumes in the acute retention group is probably multifactorial; bladder sacculation and diverticula, detrusor tone and reflux may all play a role

Catheterisation is a means by which urine is drained from the bladder. The effectiveness of this function has not been extensively studied in the male. Transvaginal ultrasound has been described in the female to obtain post-catheterisation volumes but only after the catheter had been removed (Haylen *et al*, 1989)

A dilutional method is described whereby the post-catheterisation residual volume may be obtained with a catheter *in situ*. The volumes obtained by this technique were used to compare 2 groups of patients commonly encountered in urological practice.

Patients and Methods

The study group comprised 15 men with a mean age of 64 years (range 55–72). Each was catheterised with a 16F Foley catheter with a 30 ml balloon Ten patients presented with acute urinary retention and were studied after 12 h of catheter drainage All subsequently underwent successful prostatectomy for benign prostatic hypertrophy The remaining 5 patients had permanent indwelling catheters for neurological urinary incontinence and presented for a routine change of catheter These patients were investigated with their old catheter *in situ* after checking that the balloon was filled with 30 ml of water.

The residual volume was calculated by a dilutional method. The patient lay in the supine position. The catheter was disconnected from the drainage system and any residual urine in the catheter lumen allowed to drain into a sterile bowl. A known volume of normal saline was instilled into the bladder, sufficient to enable free mixing with a bladder syringe. This volume varied between 30 and 100 ml. A 10-ml sample was then obtained. This process was repeated to obtain a second 10-ml sample of urine The 2 samples were then analysed for urea concentration. If any spillage of urine occurred the procedure was abandoned.

The volumes of normal saline instilled and the volumes obtained for samples were recorded. These volumes and the urea concentrations of the samples were used to calculate the post-catheterisation residual volume using the following formula:

$$\frac{A\,(S-V1)+B\,(V1-S+V2)}{A-B} \qquad (1)$$

A = Concentration of urea in the first sample.
B = Concentration of urea in the second sample.
V1 = Volume of normal saline in the first instillation.
V2 = Volume of normal saline in the second instillation.

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S = Volume of diluted urine taken for the first sample.

Results

The mean post-catheterisation volumes for patients who presented in acute retention was 98 53 ml (range 40–385). Patients who presented for a change of their long-term catheter had a mean post-catheterisation volume of 14.84 ml (range 3.5–36 8) (Fig.). The difference in volumes between these 2 groups was compared using Students *t* test and was statistically significant ($P<0.01$).

Discussion

Quantification of residual urine using catheterisation is important in the assessment of many urological problems (Di Mare *et al.*, 1966) It is generally believed that the catheter effectively drains the bladder such that the volumes obtained by this method are used as standards against which other methods of assessing residual volume are compared Our results indicate that urine remains in the bladder when there has been a catheter *in situ* for an adequate period to allow drainage. This post-catheterisation residual volume has not been extensively studied, although it has been implicated as a factor in the aetiology of urinary tract infection in catheterised patients (Kelly and Griffiths, 1983).

A method of measuring this volume in women has been described using the technique of transvaginal ultrasound (Haylen *et al*, 1989). The method described here can be applied to both sexes, is simple, painless and does not require the catheter to be removed.

It has been demonstrated using fluoroscopy that 26% of patients will have urine remaining in the bladder immediately after catheterisation (Stoller and Millard, 1989). Bladder drainage was then improved by employing certain manoeuvres such as suprapubic pressure, advancing the catheter back and forth, syringe suction and twisting the catheter. It is unlikely that these factors can account for the volumes noted in this study when a substantial amount of time had been allowed for bladder drainage The results demonstrate that the effectiveness of a catheter in draining a bladder can vary with the clinical situation. This implies that individual bladder factors play a role in determining the post-catheterisation residual volume

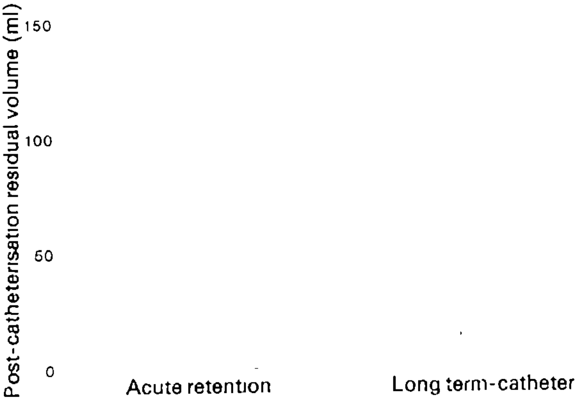

Fig. Mean volumes of urine following catheterisation

The catheter is also a factor to consider Stoller and Millard (1978) commented that some catheters tented up the dome of the bladder, thus creating a potential space to trap urine The reason why patients presenting in acute retention should have larger post-catheterisation volumes than patients with chronic indwelling catheters, when all were catheterised with the same catheter, is unclear. One aspect may be an inability of the detrusor to obliterate the space between the bladder urothelium and the catheter balloon. Patients with bladder outflow obstruction are more likely to have bladder sacculation and diverticula which may prevent this apposition and create potential spaces to trap urine. Other factors may include detrusor tone and vesicoureteric reflux, although in this study no patient had this latter problem

It is clear that the bladder and catheter play an important part in determining the post-catheterisation residual volume. It is unusual that so little research has investigated this fundamental function of urinary catheters. Clearly it is an area that needs to be explored further

Acknowledgements

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The Author

S F Purkiss, FRCSE, FRCS, formerly Surgical Registrar, Department of Surgery, Princess Margaret Hospital Now Clinical Research Fellow, Surgical Unit, Fourth floor, Alexandra Wing, The London Hospital, Whitechapel, London E1 1BB

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Cell Cycling in Bladder Carcinoma Determined by Monoclonal Antibody Ki67

K. MELLON, D. E. NEAL, M. C. ROBINSON, C. MARSH and C. WRIGHT

Departments of Urology and Pathology, Freeman Hospital, Department of Pathology, Royal Victoria Infirmary, University Department of Surgery, Newcastle upon Tyne

Summary—Current methods of predicting prognosis in transitional cell carcinoma of the bladder fail to provide consistently reliable information about future tumour behaviour. The monoclonal antibody Ki67 recognises an antigen present in actively dividing cells and Ki67 reactivity has been shown to correlate with conventional prognostic indicators in several tumours. In this study, Ki67 antibody was used to determine the proportions of cells undergoing active division in 26 transitional cell carcinomas of the bladder.

The proportion of cells stained in muscle invasive tumours (12.3 ± 5.4%) was significantly greater than in superficial tumours (4.3 ± 1.9%) and poorly differentiated tumours showed significantly greater proportions of cells staining compared with well or moderately well differentiated tumours.

These results show that Ki67 reactivity correlates with high tumour stage and poor differentiation. Ki67 staining provides an easy method of determining tumour cell turnover that might provide additional prognostic information.

At first presentation, approximately 30% of bladder cancers are found to invade the bladder muscle and usually require aggressive treatment. The remainder (pTa, pT1) do not invade muscle, but about 70% of these recur following resection and 10 to 20% will undergo stage progression (Greene *et al.*, 1973; Anderstrom *et al.*, 1980). The heterogenous nature of bladder cancer provides a challenge to the clinician, who must try to identify those patients with tumours which are likely to behave aggressively.

Clinical staging and histopathological grading are the mainstay of assessing prognosis in bladder cancer. However, these parameters often fail to predict accurately a tumour's future progress. New biological variables of potential prognostic value are therefore being tested.

Studies of tumour cell kinetics are potentially of great value since they probably reflect a tumour's biological activity and may define its potential clinical aggressiveness. However, as yet there has not been an easy way to measure the proliferative rate of a tumour. The discovery of the monoclonal antibody Ki67 (Gerdes *et al.*, 1983) appears to provide a relatively simple method of determining proliferative rates. Ki67 antibody recognises an unknown nuclear antigen expressed in the S, G_2 and M phases of the cell cycle but which is absent in G_0 phase. Cells in the early stages of transition between G_0 and G_1, *i.e.* G_{1I} and first G_{1A}, lack the Ki67 antigen, whereas G_1 cells after mitosis are Ki67 positive (Gerdes *et al.*, 1984). The immunohistochemical determination of the growth fraction of a tumour using Ki67 antibody may prove to be a rapid and simple technique that provides additional prognostic information and helps to identify high risk groups of patients.

Patients and Methods

A total of 26 patients (20 men, 6 women, mean age 62.8 ± 12.8 years) with transitional cell carcinoma

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of the bladder were studied. Of these, 15 had superficial tumours (pTa/pT1) and 11 had muscle invasive tumours (pT2/T3/T4). There were 2 grade 1, 13 grade 2 and 11 grade 3 tumours.

Samples of tumour were obtained in the usual way using the resectoscope. They were snap frozen in isopentane cooled to −180°C with liquid nitrogen, wrapped in foil and stored in liquid nitrogen until processed.

Immunohistochemistry

Cryostat sections (5 microns thick) were air dried on to 0·01% poly-l-lysine coated slides and were fixed in cold acetone for 20 min. They were then treated with Tris buffered saline (TBS, pH 7.6) for 10 min followed by normal rabbit serum (NRS) for a further 10 min. The sections were incubated for 60 min with Ki67 antibody (DAKO Ltd., High Wycombe, London), diluted 1:50 with NRS/TBS (ratio 1:4). They were then rinsed twice in TBS before incubation for 30 min with peroxidase conjugated rabbit-anti-mouse antibody (DAKO Ltd), diluted 1:20 with NRS/TBS. Sections were washed twice more and peroxidase activity was then developed using hydrogen peroxide-diaminobenzidine solution (Graham and Karnovsky, 1966). Finally, the sections were washed in water, counterstained with Carazzi's haematoxylin, dehydrated and mounted.

A negative control was performed for each tissue section by omission of the primary anti-serum. Tonsillar tissue was used as the positive control.

The proportion of tumour cell nuclei staining with Ki67 antibody was assessed with the aid of a 0.09 mm^2 eye piece graticule (E11A, 21 mm, Graticules Limited). Nuclei in morphologically malignant cells were considered positive for the Ki67 antigen when they showed dark brown granular staining. Random fields in well preserved areas of tumour within the cryostat sections were examined and an average of 2000 malignant cells (range 1400–2700) were counted in each case. In some tumours there was patchy weak cytoplasmic staining with Ki67 but this did not present difficulties in interpretation.

Routine histological sections stained with H and E were available in all cases to confirm the distribution of tumour cells within the sections.

Statistical analysis

Data are reported as means ± 1 standard deviation. Differences between 2 groups were assessed by means of the Mann-Whitney test. A P value of <0.05 was considered significant.

Results

Assessment of Ki67 nuclear positivity was relatively straightforward in the well differentiated and moderately well differentiated transitional cell carcinomas, as the tumours were generally well preserved with little necrosis (Fig. 1).

In the poorly differentiated tumours there was a higher incidence of necrosis leading to poorer quality frozen sections. Nevertheless, the clear brown staining of Ki67 positive nuclei was clearly evident in areas of viable tumour (Fig. 2).

Figure 3 shows the percentage of cells stained by Ki67 for tumours of different stage (Fig. 3A) and different grade (Fig. 3B). The number of cells stained in the high stage tumours (mean ± SD, $12.3 \pm 5.4\%$) was significantly greater than in the superficial tumours ($4.3 \pm 1.9\%$; $P<0.01$). Poorly differentiated tumours showed significantly greater staining ($12.2 \pm 5.6\%$) compared with moderately or well differentiated tumours ($4.4 \pm 2.1\%$; $P<0.01$).

Discussion

In attempting to classify patients with bladder cancer, particular attention must be paid to 2 main groups: those who will develop multiple recurrent tumours of similar stage to the initial lesion and those who initially present with superficial bladder

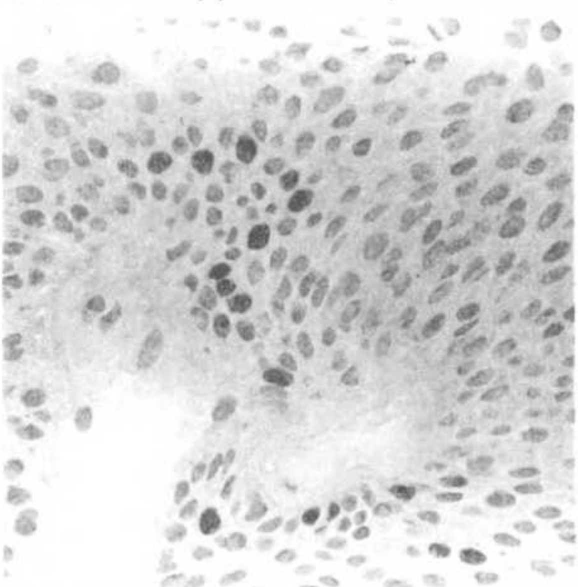

Fig. 1 Well differentiated non-invasive (pTa) transitional cell carcinoma of the bladder showing few positively stained nuclei (Immunoperoxidase stain for Ki67 counterstained with Carazzi's haematoxylin × 310).

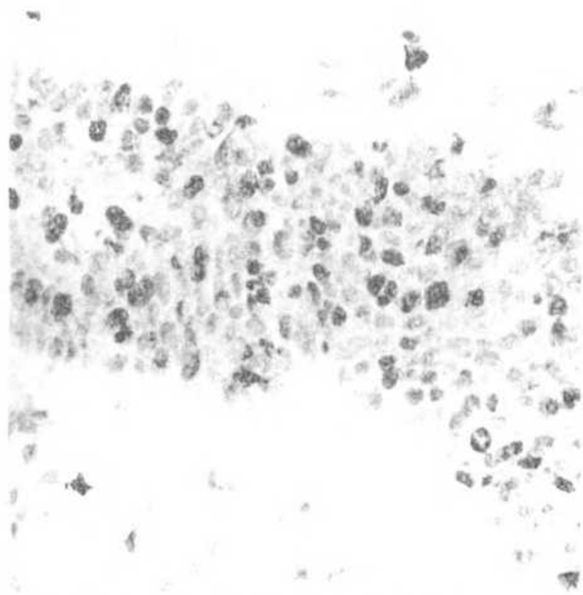

Fig. 2. Poorly differentiated invasive (pT3) transitional cell carcinoma of the bladder showing many positively stained nuclei (immunoperoxidase stain for Ki-67, counter-stained with Carazzi's haematoxylin; bar = 5μm).

cancer (pTa, pT1) but who will later develop muscle invasive disease. Several tumour characteristics are already known to indicate lesions which are likely to behave badly. Tumours with microscopic evidence of invasion of the lamina propria (pT1 or pT2) are associated with a worse prognosis (Anderstrom *et al.*, 1980). Many reports emphasise the importance of histopathological grade in predicting prognosis (Lutzeyer *et al.*, 1982; Heney *et al.*, 1983). However, all grading systems are based on subjective assessment and lack of reproducibility is therefore an inherent problem (Busch *et al.*, 1977; Ooms *et al.*, 1983).

Mucosal abnormalities both at the margin of the tumour and in selected biopsies from apparently normal urothelium have important implications for prognosis. Althausen *et al.* (1976) observed that of the 30% of patients with initially superficial disease who developed muscle invasive disease within 5 years, the majority had some mucosal abnormality in the urothelium immediately adjacent to the primary lesion, either urothelial atypia or carcinoma *in situ*. Several investigators have shown the ominous significance of carcinoma *in situ*, and possibly of epithelial dysplasia, in biopsies of normal-looking urothelium elsewhere in the tumour-containing bladder (Koss *et al.*, 1977; Murphy *et al.*, 1979; Smith *et al.*, 1983; Wolf *et al.*, 1987). Diffuse epithelial involvement may be reflected in multiple deposits of superficial disease. As well as being associated with tumour recurrence this too has been claimed to correlate with disease progression (Heney *et al.*, 1982; Lutzeyer *et al.*, 1982; Fossa *et al.*, 1985).

Large tumours and recurrent tumours increase the likelihood of stage progression (Heney *et al.*, 1983; Fossa *et al.*, 1985 respectively). The presence on the tumour cell of receptors for peptide growth factors may be a future means of detecting tumours likely to progress (Neal *et al.*, 1990).

Much attention has been paid to the antigenic characteristics of the urothelial tumour cell and prognosis. Normal cell surface antigens may be deleted or abnormal ones expressed by the tumour cell. Clinical significance has been reported with blood group antigens (Decenzo *et al.*, 1975; Lange and Limas, 1984), beta 2 microglobulin (Walton *et al.*, 1986), Thomsen-Friedreich antigen (Summers *et al.*, 1983) and epithelial membrane antigen (Pocock *et al.*, 1985).

The determination of the percentage of proliferating cells may be of prognostic value and may become an important factor in choosing appropriate treatment (Gerdes *et al.*, 1987; Hall *et al.*, 1988). Previously, proliferative rates have been estimated by measurement of the number of mitotic figures; this is slow and difficult. Various other approaches have been tried. $[^3H]$ thymidine can be given to the patient and the subsequent radioactivity of the tumour cells assessed using autoradiography. However, this method is difficult, requires at least several days of autoradiographic exposure and although the total amount of radiation is negligible the effect of incorporation into normal tissue is unknown. In much the same way, the halo-pyrimidine bromodeoxyuridine (BrdU) can be administered. Like $[^3H]$-thymidine, BrdU is incorporated into DNA during its synthesis and cell nuclei containing BrdU can then be detected using a monoclonal antibody technique. Although only small amounts of BrdU are used in this method, it is known to be cytocidal and teratogenic in higher doses. Modifications of these methods include incubation of fresh tissue samples with $[^3H]$-thymidine or BrdU, but the effectiveness of these in labelling dividing cells is unknown. Flow cytometry also provides a technique for assessing actively dividing cells but requires expensive equipment and personnel as well as the preparation of a single cell suspension.

Using Ki67 antibody, the proliferative rate can be rapidly calculated with no risk to the patient. The technique does, however, depend upon the preparation of frozen sections which are of good

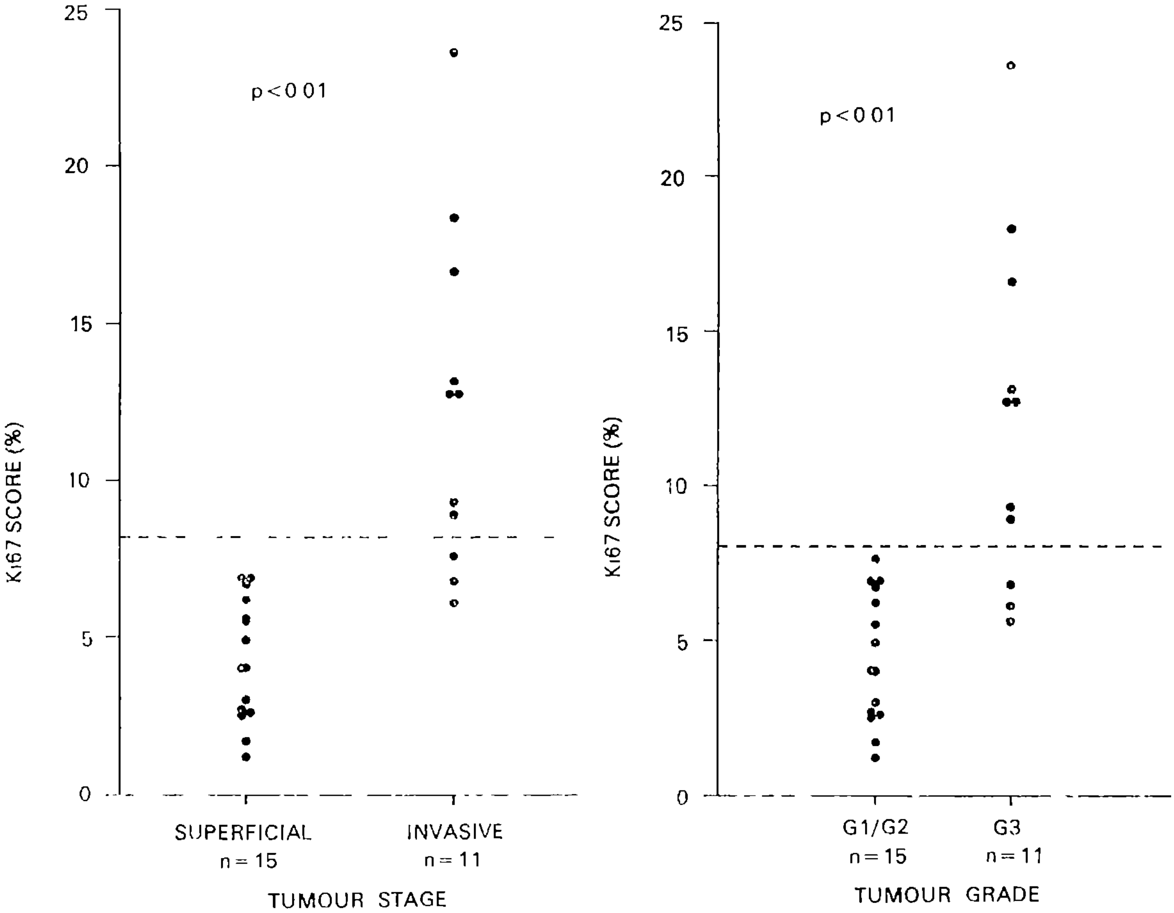

Fig. 3 (A) Ki67 score (%) related to tumour stage (B) Ki67 score (%) related to tumour grade

quality and which contain sufficient numbers of cells This should be well within the scope of most laboratories. In a wide range of normal and neoplastic tissues, the growth fraction determined using Ki67 antibody correlates well with cell proliferation rates determined using radioactively labelled DNA precursors (Gerdes *et al*, 1983) The results from the present study are similar to those of Nemoto *et al* (1988) who, using BrdU, calculated the average S phase fractions for non-invasive and invasive tumours to be 9 8 and 20.0% respectively The clinical significance of these figures has yet to be clarified but Nemoto *et al* concluded that bladder cancers with S phase fractions > 10% appeared to grow faster and to be more invasive. Gerdes *et al.* (1988) determined the growth fractions in a series of 160 breast carcinomas using Ki67 antibody and found that there was some dissociation between the measured growth fraction and histological tumour grading, although these parameters correlated overall It thus seems possible that this technique may predict the response to treatment and prognosis of patients with tumours of the same grade or stage.

The results from this study show that in bladder cancer, Ki67 growth fraction is associated with conventional prognostic indicators Further studies are now necessary to define the precise role of Ki67 as a prognostic marker.

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The Authors

K Mellon, FRCS, Urology Research Registrar
D F Neal, MS FRCS, Senior Lecturer and Consultant Urologist
M C Robinson MRCPath, Consultant Pathologist
C Marsh, Senior MLSO
C Wright, MB, BS, Lecturer in Pathology

Requests for reprints to D F Neal Department of Urology Freeman Hospital Newcastle upon Tyne NE7 7DN

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Superficial Bladder Cancer in Patients under 40 Years of Age. Efficacy of Topical Prophylaxis

J. FLAMM

Department of Urology, Wilhelminenspital, Vienna, Austria

Summary—In patients under the age of 40 years with primary superficial bladder cancer the efficacy of adjuvant topical treatment was the same as in elderly patients (recurrences 23%, progression rate 8%). Patients should therefore be treated on the basis of stage and grade of the tumour regardless of their age.

The peak incidence of superficial transitional cell carcinoma (STCC) of the bladder usually occurs in the sixth decade. In the under-40 age group, most studies have suggested that these patients suffered from the same disease as older patients (Fitzpatrick and Reda, 1986; Chang and Ma, 1987; Kurz *et al.*, 1987; Stokes and Kelly, 1987).

The aim of the present study was to evaluate the efficacy of topical treatment in 23 younger patients.

Patients and Methods

All patients (age range 26–39 years) underwent transurethral resection (TUR) of the tumour. The tumours were classified as pTa to pT1, grades 1 to 3 according to the International Union Against Cancer (1978) and the World Health Organisation.

Since 1976, patients with STCC have received adjuvant topical immunotherapy or chemotherapy (BCG, cisplatin, doxorubicin, ethoglucid). All were followed up for at least 5 years.

Results

Recurrence

Six of the 23 patients with primary STCC had a recurrence of tumour (30% after TUR alone and 23% after TUR and topical treatment). The mean tumour-free interval after TUR alone was 13 months (range 5–28) and after TUR with topical treatment 24 months (range 9–48) (Fig.). The recurrence rate in the group with TUR alone was 0.7 and in the group with adjuvant treatment 0.5%.

Progression

Three patients showed progression in the recurrence (2 after TUR alone and 1 after topical treatment). One showed severe progression in stage and grade with development of carcinoma *in situ*. In this case a cystectomy was performed.

Discussion

STCC occurring when the patient is 40 years old or

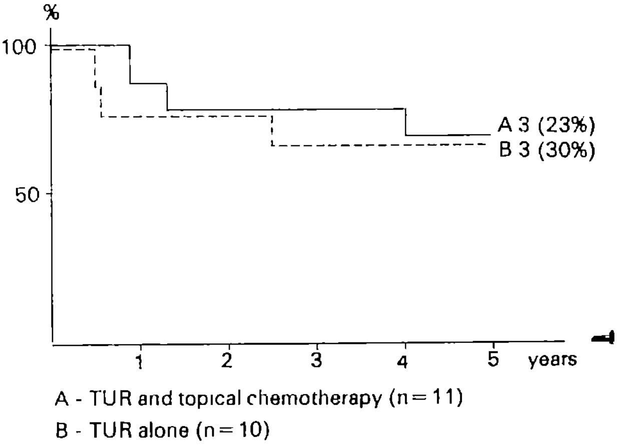

Fig. Interval to first recurrence in patients less than 40 years of age with primary STCC of the bladder.

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less shows little difference from the disease as it affects older patients.

Even the subgroups are small and adjuvant topical treatment in younger patients seems to be as effective as in elderly patients The time to first recurrence is longer and the recurrence rate lower in the group with adjuvant therapy.

All treatment should be based on the pathological condition regardless of the patient's age

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The Author

J Flamm, MD, Urologist Department of Urology, Wilhelminenspital Montleartstrasse 37 A 1171 Vienna, Austria

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Assessment of Factors Influencing the Outcome of Radiotherapy for Bladder Cancer

S. E. DAVIDSON, R. P SYMONDS, M. P SNEE, S UPADHYAY, T HABESHAW and A. G. ROBERTSON

Beatson Oncology Centre, Western Infirmary, Glasgow

Summary—The results of treatment of 709 patients with carcinoma of the bladder are reported Inclusion of the pelvic lymph nodes in the treatment volume failed to lead to any improvement in survival. The factors influencing survival were stage, tumour histology and differentiation. The presence of tumour at follow-up cystoscopy at 3 months was of great prognostic significance

The results of treatment of invasive bladder carcinoma remain disappointing. In an attempt to improve local control and survival in patients treated by radiotherapy in Glasgow, it was decided to include the pelvic lymph nodes within the irradiated volume for part of the treatment schedule and gradually increase the radiation dose received by the bladder tumour The basis for this change in technique was that spread to the pelvic lymph nodes is common and the response of transitional cell carcinoma of the bladder to radiation is dose-dependent. Wallace and Bloom (1976) showed that 40 to 50% of patients with T3 tumours treated by cystectomy had lymph node metastases Relatively modest doses of radiation (4000 cGy in 4 weeks) given prior to cystectomy have been shown to produce substantial bladder tumour regression with "down staging" of the primary tumour and sterilisation of the nodal deposits (Bloom *et al.*, 1982) As Morrison (1975) demonstrated a marked correlation between tumour control and radiation dose, with a steep dose response curve, a relatively small increase in the dose received by the primary tumour may be significant in terms of local control. We have compared, retrospectively, local control and survival of sequential groups of patients receiving radiotherapy to the bladder alone, or the pelvic lymph nodes for part of the treatment schedule, and doses of 6000, 6250, 6400 and 7200 cGy to the primary tumour. We also examined the effect of tumour stage, histology and degree of differentiation, patient's sex and age upon the results of treatment.

Patients and Methods

From 1978 to 1984, 709 patients with carcinoma of the bladder were treated with potentially curable doses of radiotherapy. Initial staging was by examination under anaesthesia and cystoscopy by the referring urologist according to UICC (1978) criteria All patients were treated using a 4 Mev linear accelerator. In the early part of the study all patients were treated according to individual consultant preference with doses of 5000 to 6000 cGy over 4 to 6 weeks The treatment schedule most commonly used was 6000 cGy in 30 fractions in 6 weeks From 1982, patients were treated by agreed regimens in an attempt to find if increasing the radiation dose to the bladder led to increased local control Doses of 6250 and 6400 cGy were given in 30 fractions in 6 weeks.

The patient's sex, tumour stage and degree of differentiation are listed according to radiation dose in Table 1 Except for larger numbers of patients with T4 tumours receiving total doses of less than 6000 cGy, the distribution of characteristics is remarkably similar between each group. 395 patients received treatment to the pelvic nodes Treatment was given using a 4-field technique for 4

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weeks, followed by a boost to the bladder over 2 weeks. Initially, the dose given to the pelvic nodes was 4000 cGy. In the case of patients receiving bladder doses of 6250 and 6400 cGy, the nodal dose was increased to 4250 cGy. The average treatment volume was 14 × 14 × 10 cm. When planning treatment to the bladder alone, either as a boost or the sole treatment volume, the bladder was outlined radiologically after instillation of contrast medium through a catheter. The whole bladder was treated with a margin of 1–2 cm of normal tissue using an anterior and 2 anterior oblique fields. The average boost volume was 8 × 8 × 8 cm. Computer assisted tomography was not used at that time.

In the early part of the study, 186 patients were allowed a gap of 2 to 3 weeks half-way through treatment. At this time it was thought that a split course schedule reduced the acute toxicity of radiotherapy without loss of efficacy (Sambrook, 1962). Most of these patients received 6000 cGy in 30 fractions. The total bladder dose in 14 patients was 7200 cGy. These patients were treated with a boost to the bladder of 3200 cGy in 10 fractions in 2 weeks after a pelvic dose of 4000 cGy.

All patients have had at least 30 months of follow-up. Survival has been calculated from the first day of treatment. Statistical analysis has been performed using the actuarial life table method and the log rank test.

Results

The median age of patients in this series was 68 years. The uncorrected 5-year survival rate was 24.7%. As this was an elderly population, a significant proportion of patients died from intercurrent disease (mainly cardiovascular disease) rather than bladder cancer (Table 2). When non-cancer deaths are excluded, the actuarial 5-year survival rate rises to 31.1%. Unless otherwise stated, non-cancer deaths have been excluded in the subsequent analysis of survival data. As one would expect, tumour histology, stage and degree of differentiation were the most important factors governing prognosis. Patients with transitional cell tumours fared better than those with squamous tumours, the 5-year survival rate being 32.6 and 11.2% respectively ($P=<0.001$). an important factor influencing survival of these patients was the advanced stage at presentation of squamous tumours. Most patients (44/46) presented with T3 or T4 tumours. Overall, increasing tumour stage has an adverse effect upon prognosis (Fig. 1). Five-year survival by stage was as follows: T1 (86.9%), T2 (49.1%), T3 (27.7%) and T4 (2.3%). When intercurrent deaths were included, survival fell as follows: T1 (70.5%), T2 (40.2%), T3 (21.4%) and T4 (1.8%). The degree of tumour differentiation had a significant effect on survival, the 5-year survival of patients with well differentiated tumours (G1) being 41.8%, moderately well (G2) 28.3% and poorly differentiated tumours 25.5%. The overall chi-square was 11.56 (2 df) ($P=0.011$).

Although more men (505) than women (204) were treated, the 5-year survival rate of men (29%) and women (36%) was similar ($P=0.194$). In contrast, increasing age had an adverse prognostic effect irrespective of whether intercurrent deaths were included or excluded (Table 3).

Treatment of pelvic lymph nodes did not impart any advantage on survival. Indeed, patients receiving nodal irradiation had a significantly worse outlook, 5-year survival being 26.3% in contrast to 37.3% for those receiving treatment to the bladder

Table 1 Distribution of Tumour Stage, Degree of Differentiation and Patient's Sex, by Radiation Dose

		<6000	*6000*	*6250*	*6400*	*7200*	*Total*	*%*
Stage T1		4	28	0	1	1	34	4.8
T2		32	123	11	19	4	189	26.6
T3		94	172	14	39	9	328	46.3
T4		89	48	7	14	0	158	22.3
Degree of differentiation	G1	57	88	12	8	1	166	23.4
	G2	57	98	7	26	5	193	27.2
	G3	99	152	11	33	5	300	42.3
	Gx	6	33	2	6	3	50	7.1
Sex. Male		140	281	22	54	8	505	71.2
Female		79	90	10	10	6	204	28.8
Total		219	371	32	73	14	709	100

Table 2 Causes of Death

	No. of Patients	*Percentage deaths*
Local recurrence only	115	23.4
Metastases only	63	12.8
Local recurrence plus metastases	227	46.1
Non-bladder cancer	86	17.5
Treatment-related deaths	1	0.2
Total	494	100

No. of patients alive 217.

Table 3 Actuarial 5-Year Survival by Age

Age (years)	*Percentage 5-year survival including non-cancer deaths*	*Percentage 5-year survival excluding non-cancer deaths*
<60	35.5	39.3
60–65	26.3	31.8
65–70	27.5	32.5
>70	18.1	26.4

alone ($P = 0.003$). This difference in survival probably reflects a tendency to treat early stage tumours by irradiation of the bladder only and to include the nodes when treating more advanced cases. As shown in Figure 2, stage for stage there was no difference in survival regardless of whether the nodes were irradiated or not.

Recurrence-free survival and survival according to radiation dose are shown in Figures 3 and 4. The local control and survival of patients receiving 6400 and 6000 cGy given in 30 fractions over 6 weeks are remarkably similar (Fig. 3). The poor results seen in the small group of patients receiving 7200 cGy may be due in part to the 2 to 3 week gap in their particular treatment schedules. A gap in treatment significantly worsens the results (Fig. 5). The 5-year survival of patients treated continuously was 35.0%, in comparison to 21.7% when a gap of 2 to 3 weeks was permitted during treatment ($P = 0.001$).

Late radiation morbidity was classified as mild, moderate or severe. Symptoms such as frequency or dysuria were classified as mild if the patient was managed as an out-patient. If admission was required for investigation or treatment (*e.g.* cystoscopy for haematuria), symptoms were graded as moderate. Patients requiring operative intervention such as bowel resection or cystectomy were graded as having severe late effects. Radiation morbidity was similar at each dose level (Table 4). Those patients receiving nodal irradiation had an increased incidence of severe complications, 9.6% compared with 4.3% of those receiving bladder irradiation alone. There was 1 treatment-related death. This patient had a T4 tumour and was aged 81 years.

Cystectomy was carried out as a salvage procedure in 78 patients with recurrent disease and in 7 cases for treatment-related complications. Although 3 patients had major post-operative complications, there were no deaths following cystectomy. The 5-year survival of this group of patients was 33%.

The presence of tumour at follow-up cystoscopy 3 months after treatment was of great prognostic significance. The 5-year survival rate was 17.3% against 54% of those found to be tumour-free (Fig. 6).

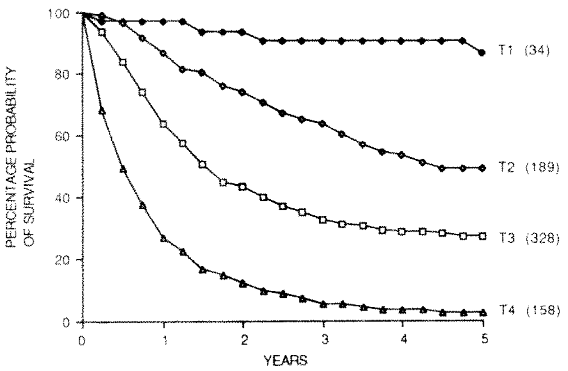

Fig. 1 Percentage probability of survival by tumour stage (intercurrent deaths excluded). Figures in brackets show the number of patients in each T stage group.

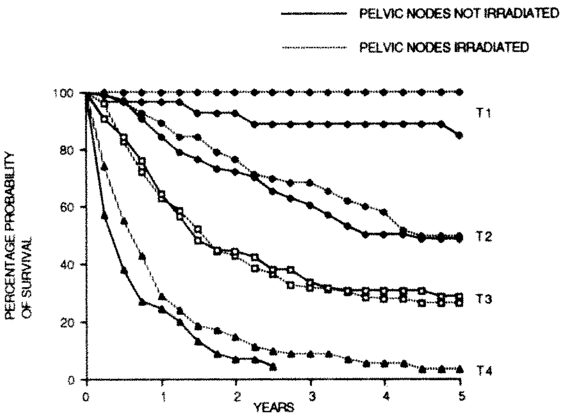

Fig. 2 Effect of pelvic lymph node irradiation upon survival in each T stage.

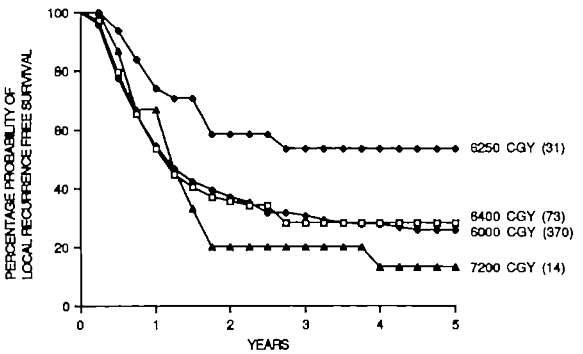

Fig. 3 Effect of radiation dose upon percentage probability of local tumour control.

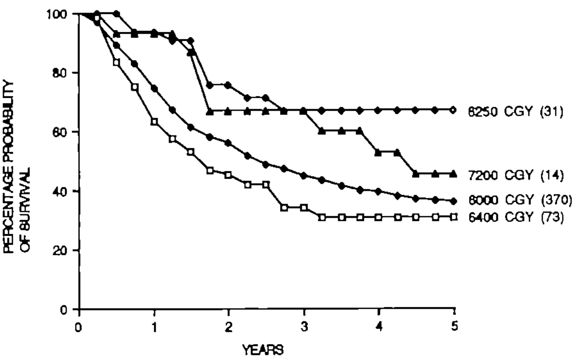

Fig. 4 Effect of radiation dose upon percentage probability of survival

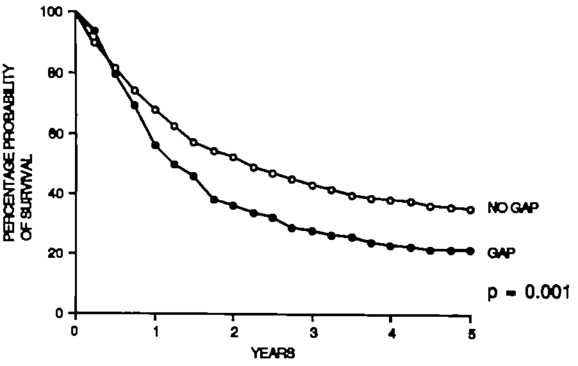

Fig. 5 Effect of gap (2–3 week rest in treatment) upon outcome

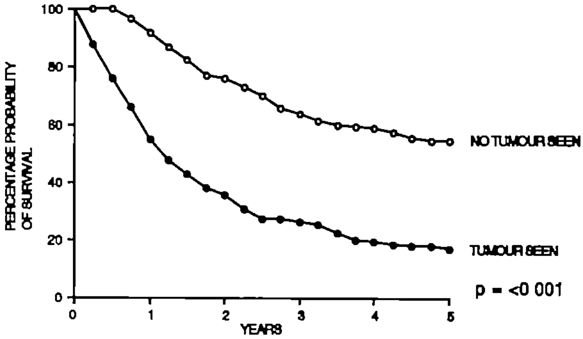

Fig. 6 Prognostic effect of presence of tumour at first cystoscopy 3 months after radiotherapy.

Discussion

It is well known that there are 2 groups of bladder tumours with different prognoses. The first is composed of well differentiated tumours which do not invade muscle and can be controlled by transurethral resection and have a good prognosis. The second consists of tumours which invade muscle, tend to be poorly differentiated and are more likely to recur after transurethral resection. These tumours are likely to metastasise and consequently have a worse prognosis. In Britain these patients are more likely to be treated by radiotherapy. The overall survival in this series (31.1%) is similar to that of other British series. Preoperative radiotherapy to the pelvis prior to cystectomy has improved survival, which has been attributed to sterilisation of spread to regional lymph nodes (Van der Werf Messing *et al.*, 1982).

A similar increase in survival would perhaps be expected when pelvic nodes are irradiated as part of a radical radiotherapy schedule, but we have failed to show any improvement in survival using this approach. Treatment to a larger volume does increase the complication rate, 9.6% with severe complications compared with 4.3% when treatment is given to the bladder alone. The importance of pelvic node irradiation has not been tested in a controlled study. Only one other retrospective study has compared treatment of the pelvis with irradia-

Table 4 Incidence and Severity of Late Complications of Radiotherapy by Dose

Dose (cGy)	*None*	*Mild*	*Moderate*	*Severe*	*Death*	*Total*
6000	144	138	74	14	1	371
6250	20	3	7	2	0	32
6400	48	7	15	3	0	73
7200	7	4	3	0	0	14

tion of the bladder alone (Goffinet *et al.*, 1975). No differences in survival were seen between the 2 groups except that stage D (T4) tumours had a short-term increase in survival.

A small improvement in local control was seen with the increase in radiation dose, although no increase in overall survival was demonstrated. Complications were similar for all 4 dose levels. What is striking is that biological differences such as age, tumour stage and grade are the factors which determine outcome rather than differences in radiotherapy technique.

As with other British series (Rothwell *et al.*, 1985), the median age in this series was 68 years and 16% have already died of intercurrent disease. Increasing age adversely affects prognosis and this has been shown in other series from Edinburgh (Duncan and Quilty, 1986) and the London Hospital (Blandy *et al.*, 1980).

The most important prognostic factor is the T stage. T4 tumours in this series fared poorly. Most of the T1 tumours were referred after recurrence following endoscopic surgery. The good survival figure (87%) reflects the relatively good prognosis for this tumour stage whatever treatment is used, but it is noteworthy that half of the patients had poorly differentiated lesions. It can be difficult to distinguish between T2 and T3 tumours (Chisholm *et al.*, 1980) but the distinction made by the referring urologists seems to be of prognostic value, with a difference in survival of 22% at 5 years between the 2 stages. Patients with well differentiated tumours fared better than those with poorly differentiated lesions. These results reinforce the view that patients with poorly differentiated tumours or those with muscle invasion benefit from early referral for radiotherapy.

A negative cystoscopic examination 3 months after radiotherapy is a good prognostic finding (5-year survival 54.6%) and this is in agreement with other series (Blandy *et al.*, 1980; Abratt *et al.*, 1983; Duncan and Quilty, 1986). Salvage cystectomy in selected patients proved to be a worthwhile procedure, with a 5-year survival rate of 33% and no operative deaths. Since the 5-year survival of patients with visible tumour 3 months after radiotherapy is only 17.3%, perhaps cystectomy should be considered at an early stage if patients are free of metastases and fit to undergo this operation.

Local control in the treatment of bladder cancer by radiotherapy is still a major problem. In this series, 23% of patients died with local disease only, 46% with local disease and metastases and 13% with metastases alone. The addition of chemotherapy to radiotherapy may increase local control. Data derived from this study may be useful in the design of multicentre chemotherapy/radiotherapy studies. Differences in radical radiotherapy schedules are probably of little importance; these results are similar to those published from Edinburgh (Quilty *et al.*, 1985) using a 4-week rather than a 6-week schedule. Radiotherapy should be confined to the bladder only; the inclusion of the pelvic nodes merely increases morbidity. Gaps in treatment should be avoided.

Bladder cancer in Britain is primarily a disease of the elderly. Older patients have a poorer prognosis and, of course, are more likely to die from causes unrelated to cancer. The median age of patients in chemotherapy studies tends to be a decade younger than our patients (Carmichael *et al.*, 1985; Harker *et al.*, 1985). The drugs most active against bladder cancer are cisplatin and methotrexate. Both agents are potentially toxic and are poorly tolerated unless the patient is fit and has good renal function. The conditions listed above imply that many of the patients considered for radical radiotherapy may not be suitable for trials using chemotherapy combined with radiotherapy.

Acknowledgements

We are grateful to the many urological surgeons who referred these patients for management by radiotherapy. We would also like to thank Mrs Olive Smith for help with the computerised data retrieval and analysis and Marjorie Evans for typing the manuscript.

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The Authors

S. E Davidson, MRCP, FRCR, Research Registrar, Department of Radiobiology, Paterson Institute for Cancer Research, Christie Hospital and Holt Radium Institute, Manchester

R P. Symonds, MD, FRCP, FRCR, Consultant in Radiotherapy and Oncology, Beatson Oncology Centre.

M. P Snee, MB, FRCR, Clinical Scientist and Honorary Senior Registrar, MRC Environmental Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton.

S. Upadhyay, DMRT, Radiotherapist, Safdarjang Hospital, New Delhi, India.

T. Habeshaw, FRCP, FRCR, Consultant in Radiotherapy and Oncology, Beatson Oncology Centre.

A G. Robertson, PhD, FRCR, Consultant in Radiotherapy and Oncology, Beatson Oncology Centre.

Requests for reprints to. R P Symonds, Department of Radiotherapy and Oncology, Beatson Oncology Centre, Western Infirmary, Glasgow G11 6NT.

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Cobb's Collar—a Forgotten Entity

D. CRANSTON, A. H. DAVIES and J. C. SMITH

Department of Urology, Churchill Hospital, Oxford

Summary—Cobb's collar or Moormann's ring is a stricture of the bulbar urethra which is largely unrecognised but has considerable relevance urologically as the site of congenital or post-instrumental strictures. The history, anatomy, embryology and surgical importance are reported.

Just below the external sphincter in the bulbar urethra a ridge of tissue may often be observed on urethroscopy. Occasionally this forms an occluding membrane with a small lumen and it can be observed both radiologically and endoscopically as a fibrous or membranous stenosis of the bulbar urethra. Such a stricture was described in the USA by Cobb *et al.* (1968) and has also been described by Moormann (1972) in continental Europe, where it is known as Moormann's ring. This part of the urethra has received virtually no mention in either textbooks of anatomy or urological surgery.

Case Reports

Case 1. Congenital Stricture

Mr A.P. presented in August 1989 aged 28 years with a history of a poor stream all his life and a 2-year history of enuresis and nocturia. In 1987 he had had 2 episodes of near retention but had not required catheterisation. There was no history of instrumentation or infection. On examination his bladder was palpable just below the umbilicus. Neurological examination was normal, renal function was normal and there was no hydronephrosis. Urethrocystoscopy demonstrated a tight stricture (Cobb's collar III) just below the external sphincter, which was incised with an optical urethrotome. The bladder was heavily trabeculated and contained 500 ml of urine. He passed urine well when the catheter was removed the following day. When seen in the out-patient department 6 weeks later, he had a mean flow rate of 13.2 ml/s with a peak flow of 22 ml/s His nocturnal enuresis was cured and he remains symptom-free.

Case 2. Post-operative Stricture

Mr K.A. first presented in 1985 aged 57 years with a history of prostatic outflow obstruction. Over the next 6 months his symptoms grew progressively worse and in January 1986 he underwent a transurethral prostatectomy. At this operation a slight narrowing was noted just below the external sphincter (Cobb's collar II). The catheter was removed 3 days later but had to be reinserted because of clot retention. After it was removed a second time he continued to have difficulty passing urine and had a urethrocystoscopy 6 days after the first operation. This showed a urethra almost completely obstructed at the level of Cobb's collar. The cystoscope was passed gently through the stricture. There was no prostatic obstruction. He was discharged with a catheter which was removed 2 weeks later. Two months later he needed a further endoscopy for a decreasing flow rate. A recurrent stricture was seen at the level of Cobb's collar and this was incised. The bladder neck showed a slight stenosis and this was also incised. He made an uneventful recovery and remains well.

Discussion

Cobb *et al.* (1968) were the first to draw attention to the entity of congenital stricture of the bulbar urethra. They performed retrograde urethrography and voiding cine-cystourethrography on all male patients with urinary problems over a 3-year period and found 52 cases of proximal bulbo-urethral strictures. The patients ranged in age from newborn to 59 years. The strictures were diagnosed on the

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Based on a Poster Demonstration at the 45th Annual Meeting of the British Association of Urological Surgeons in St Helier, June 1989

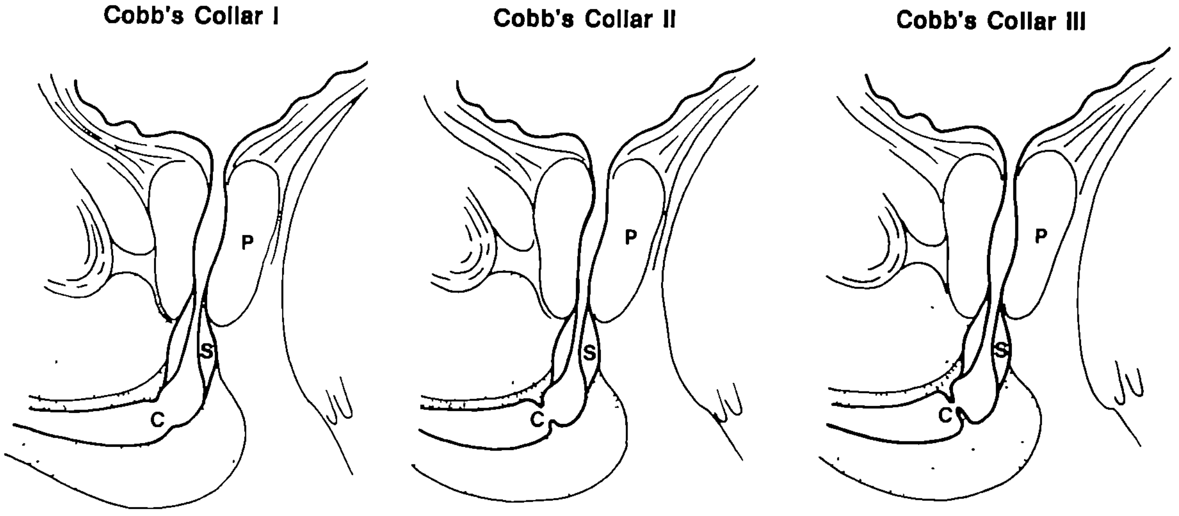
basis of symptoms and any 2 of the following 3 techniques: retrograde urethrography, calibration with bougies or cystourethroscopy. The 2 peaks of incidence occurred in infants and children and young men in their 20s. They reviewed boys under the age of 16 in an attempt to eliminate acquired strictures and found 26 strictures in the bulbar region (average age 5.5 years). Eleven of these patients presented with enuresis, 5 with infection, 6 with failure to thrive, 3 with behavioural problems and 2 with haematuria. It would be difficult to relate some of these findings to the presence of a urethral stricture on a causative basis and some of the associations may simply have been an incidental finding. However, 16 children had bladder trabeculation, 15 had a dilated prostatic fossa and 6 a secondary hydroureter.

Moorman (1972) described congenital stenosis of the bulbar urethra according to the findings on urethrography and urethroscopy in 38 males aged from 20 to 54 years and 21 males in what he described as the "prostate age". In this latter group of patients, symptoms of benign prostatic hyperplasia were present but no adenoma was found. The findings of congenital bulbar stenosis of the male urethra may be pathogenetic for several symptoms originating in the region of the urogenital junction and this stricture, which is sometimes easily dilated, will be missed by blind instrumentation.

Cobb's collar is a relatively common finding that can be seen by all urological surgeons who view the male urethra at operation rather than introducing instruments blindly into the bladder. Figure 1 and the ascending urethrogram (Fig. 2) demonstrate its site just below the external sphincter; if it is present it can appear either as a ridge of tissue (Cobb's collar I) or a definite stricture in the area described (Cobb's collar II) or even as a very tight pinhole opening (Cobb's collar III).

The absence of previous infection or instrumentation in many of these younger patients (Case 1) and the predictable site of the narrowing in the bulbar urethra suggest an embryological explanation for this stricture. Failure of complete dissolution of the urogenital membrane at the junction of the cloaca and genital groove has been suggested. However, it seems more likely that Cobb's collar is the result of a narrowing at the level of the urogenital ostium, *i.e.* the opening of the pelvic part into the phallic part of the urogenital sinus (Glenister, 1958 and personal communication) (Figs 3 and 4). It is not clear whether this could be due in part to a different blood supply to these two portions, representing a poorer supply at the site of fusion and hence predisposing to stricture formation at this point.

Cobb's collar is important surgically as an unusual cause of congenital obstruction which may occasionally cause chronic retention (Case 1) and bilateral hydronephrosis. These patients may also complain of poor ejaculation which may be dramatically improved after urethrotomy. More com-


Cobb's Collar I

Cobb's Collar II

Cobb's Collar III

Fig. 1 Sagittal section through prostate and urethra showing the area of Cobb's collar P prostate. S external sphincter. C: Cobb's collar.

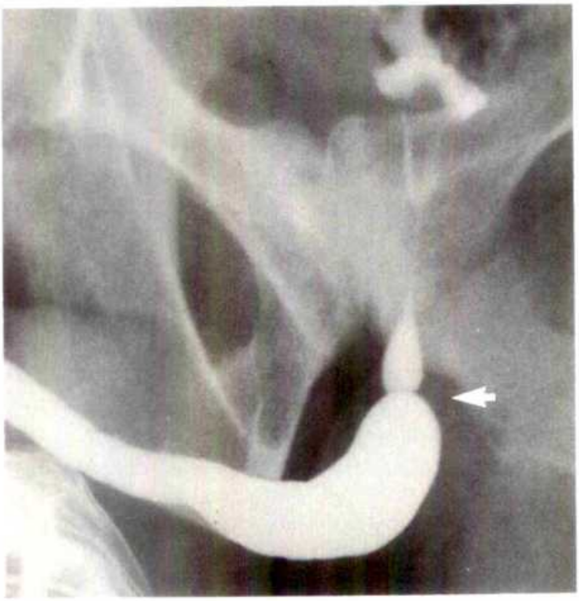


Fig. 2 Ascending urethrogram showing Cobb's collar.

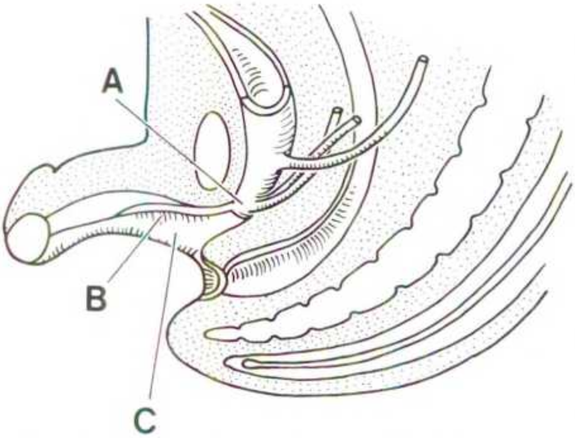


Fig. 3 Schematic sagittal section through the caudal end of a 40-mm fetus (after Glenister) (× 15). A: pelvic portion of urogenital sinus. B: Line of attachment of urogenital membrane before it disintegrates. C: Phallic portion of urogenital sinus.

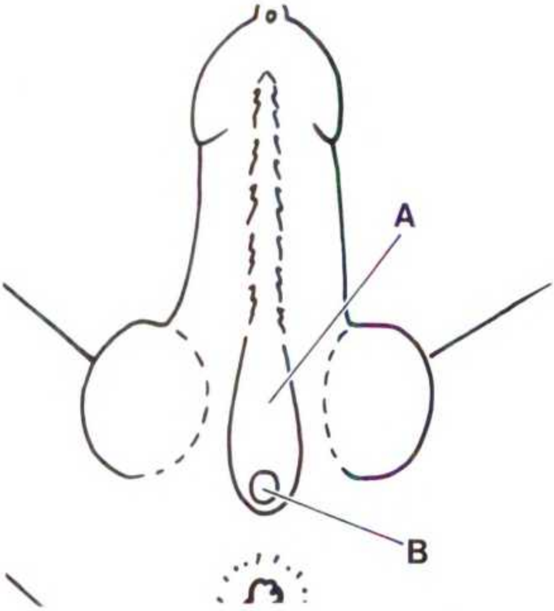


Fig. 4 Development of phallus and urethral groove as seen from below (after Glenister) (× 15). A: Open phallic part of urogenital sinus. B: Opening of pelvic part into phallic part of urogenital sinus—urogenital ostium.

monly, a stricture may form at this point following operations such as transurethral resection of the prostate. This may happen immediately postoperatively (Case 2) or later. Often the stricture can be easily dilated and it will be missed by catheterisation or blind urethral instrumentation—hence the failure of many urologists to appreciate its existence.

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The Authors

D. Cranston, DPhil, FRCS, Clinical Lecturer in Urology.
A. H. Davies, MA, FRCS, Registrar in Urology.
J. C. Smith, MS, FRCS, Consultant Urological Surgeon.

Requests for reprints to: D. Cranston, Department of Urology, Churchill Hospital, Headington, Oxford OX3 7LJ.

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Permanent External Striated Sphincter Stents in Patients with Spinal Injuries

P. J. R. SHAW, E. J. G. MILROY, A. G. TIMONEY, A. EL DIN and NAN MITCHELL

Spinal Injuries Unit, Royal National Orthopaedic Hospital, Stanmore; Institute of Urology, London

Summary—Nine patients with complete quadriplegia underwent external striated sphincter stenting with the Wallstent in place of an external striated sphincterotomy. Although suprapubic catheters were placed to provide an outlet should problems develop with the stent, they were successfully removed within 6 weeks in all but 1 patient. Complete bladder emptying with reduced voiding pressures was achieved, together with a significant reduction in the duration of hyper-reflexic contractions. Epithelialisation of the stent was almost complete within 3 months and intermittent catheterisation or endoscopy (and resection) is possible through the stent. Although this is a preliminary report of this new technique, it is hoped that sphincter stenting will provide a rapid, safe and effective method of treating high pressure hyper-reflexia and detrusor sphincter dyssynergia in quadriplegic patients.

Hyper-reflexic detrusor function is associated with external striated sphincter dyssynergia in the majority of patients with suprasacral spinal cord injury. Balanced voiding relies upon adequate spontaneous relaxation of the external striated sphincter when automatic bladder contractions occur. Subject to this occurring, condom drainage in the male will enable satisfactory bladder management in some patients with suprasacral spinal injury. The management of such patients depends upon the evaluation of bladder function by urodynamic investigation. Whenever sustained high intravesical pressures occur because of sphincter dyssynergia, bladder pressure must be reduced by the use of anticholinergic agents and bladder emptying achieved either by intermittent catheterisation or by reducing external sphincter resistance. External striated sphincterotomy by means of transurethral incision or resection of the sphincter mechanism has been the treatment of choice in this situation. Bladder neck resection was first described by Emmett, who found that the site of obstruction in the hyper-reflexic bladder was the external striated sphincter (Emmett *et al.*, 1948). Transurethral sphincterotomy was then tried by Ross *et al.* (1958). Many reports of this procedure have appeared since 1958; the results were variable and variations in technique were recommended in order to increase the success rate and reduce the complications. Because many of these severely disabled patients become continent with condom drainage systems, and because high pressure hyper-reflexia is common, sphincterotomy is often necessary to prevent the complications of high pressure obstructed hyper-reflexia, *i.e.* detrusor hypertrophy, upper tract dilatation with or without reflux, and its consequences of infection and renal damage.

The complications associated with external striated sphincterotomy, such as erectile dysfunction, haemorrhage and technical failure, could be reduced if a simpler approach to sphincterotomy could be discovered.

Following the successful use of the Wallstent (Medinvent SA, Lausanne, Switzerland) in the treatment of urethral strictures (Milroy *et al.*, 1988, 1989) we have used it in 9 selected quadriplegic patients to stent the external striated sphincter as an alternative to transurethral sphincterotomy.

Based on a Poster Demonstration at the 45th Annual Meeting of the British Association of Urological Surgeons in St Helier, June 1989

Patients and Methods

Nine patients with quadriplegia secondary to cervical spinal trauma were selected for sphincterotomy on the basis of high pressure hyper-reflexia, detrusor sphincter dyssynergia and incomplete bladder emptying. Each patient had selected permanent condom drainage as their choice of bladder management after all other methods had been discussed. Videourodynamic evaluation is routinely performed in all spinal patients in this unit and repeated whenever changes in bladder management or clinical problems develop. Each of the 9 patients was shown to have high pressure hyper-reflexia with incomplete bladder emptying and was suitable for sphincterotomy. Full informed written consent was obtained from each patient prior to insertion of the stent.

Each patient was investigated by means of combined synchronous videocystometry (Fig. 1), urinary tract ultrasound and ascending urethrography. The ascending urethrogram gave an indication of external sphincter length so that the correct length of stent could be selected, but this was later found to be unnecessary.

Under general anaesthesia, cystourethroscopy was performed to ensure that urethral appearances were normal, to wash out debris within the bladder and to allow placement under direct vision of a suprapubic catheter which was to be left in place for 6 weeks. A 16 F silicone catheter was placed via an Add-a-cath suprapubic catheter introducer (Femcare Ltd, Nottingham).

The stent was inserted under direct vision using a technique identical to that employed for urethral strictures (Milroy *et al.*, 1988). Its proximal end was placed at the level of the verumontanum and the distal end in the proximal bulbar urethra. When its position was seen to be correct the stent was opened. Stents 3 cm in length were found to be suitable for 7/9 patients. In 1 patient, 3 stents were overlapped from the bladder to the bulbar urethra to produce complete incontinence. Two patients required additional stents to complete the "sphincterotomy", 1 at the same sitting and the other 2 weeks later when bladder emptying was found to be inadequate.

Results

The mean age of the patients was 42.5 years (range 31–65). The distribution of injuries was as follows: C4 (2 patients), C5 (4), C6 (3). Each injury was associated with poor hand function which prevented intermittent self-catheterisation. Follow-up ranged from 2 weeks to 6 months. The patients were treated between 12 weeks and 10 months ago and have all reached a steady state as far as bladder emptying is concerned and have been investigated by post-stent videourodynamic studies.

A stent length of 3 cm was found to be ideal in 6/9 patients (Fig. 2). Three patients required addi-

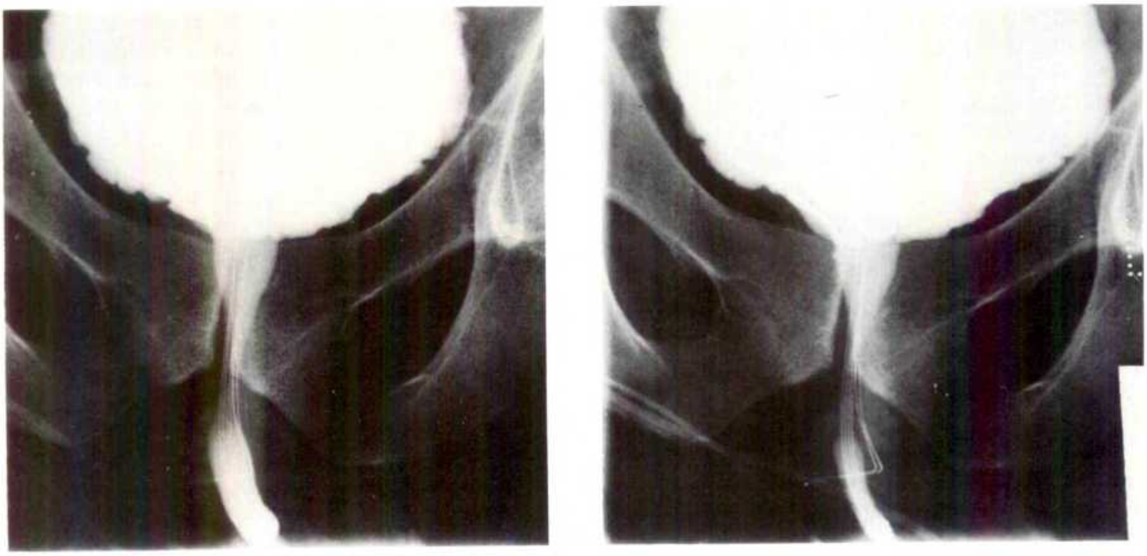

Fig. 1 Radiograph during videourodynamics demonstrating a trabeculated bladder with detrusor sphincter dyssynergia.

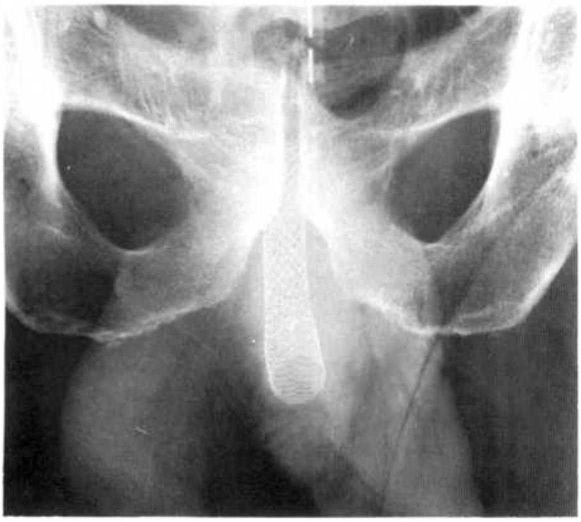

Fig. 2 Radiograph of lower external striated pelvis demonstrating a 3-cm Wallstent after insertion into the external striated sphincter.

tional stents. In 1 case the original length of 18 mm was found to be too short for the external sphincter and in another 2 cases overlapping stents were placed to overcome the problem of previous incomplete sphincterotomy.

In the third patient (No. 4), who had incomplete bladder emptying and recurrent urinary tract infection following 2 previous sphincterotomies, 3 overlapping stents were placed from the bladder neck through the external sphincter in order to produce complete incontinence. Acute septicaemia followed this procedure despite adequate pre-treatment of a urinary tract infection and per-operative antibiotic prophylaxis. He developed acute renal failure and required intensive therapy before making a full recovery. At endoscopy 10 weeks after insertion of the stents they were found to be completely epithelialised except at the ends. The stent which had been inserted across the bladder neck had retracted 1 cm into the prostatic fossa. A bladder neck incision to the level of the stent was performed and bladder emptying is now satisfactory.

Urodynamic investigations demonstrated a reduction in hyper-reflexic detrusor pressures and emptying time (Fig. 3) and good opening of the external striated sphincter (Fig. 4). When the suprapubic catheters were removed (between 2 and 6 weeks), 8 patients had improved bladder emptying (Table) with residual urine falling from a mean of 268 ml to 92. These values were obtained during urodynamic evaluation at 6 weeks and long-term residual urine values are not yet available. Patient no. 4 retains his suprapubic catheter for drainage because of incomplete bladder emptying in spite of successful outlet opening; he has persistent urinary infection and awaits urinary diversion.

The first 3 patients developed symptoms of post-operative autonomic dysreflexia, of uncertain aetiology. This settled within 1 week. This problem has not been encountered in the last 6 patients, in whom the 3 cm stent produced complete sphincter opening. There were no other complications.

Discussion

The use of external striated sphincterotomy for the relief of external sphincter obstruction (sphincter dyssynergia) in spinal injured patients was first described by Emmett *et al.* (1948). The many reports that followed (Madersbacher *et al.*, 1975; Crane and Hackler, 1978; Whitmore *et al.*, 1978; Carrion *et al.*, 1979; Ruutu and Lehtonen, 1985; Barton *et al.*, 1986) discussed a variety of surgical approaches and their successes and complications. Sphincterotomies were tried by resection of part of the external sphincter or incision at 3 and 9 o'clock, 11 and 1 o'clock or in the anteromedian position at 12 o'clock. The best results followed anteromedian sphincterotomy, where the complications of haemorrhage, infection and erectile dysfunction were lowest. This has been our policy for the last 4 years.

The difficulties arising from endoscopic incision of the external sphincter relate to technical problems and the complications that result. Complete division of the external sphincter is not easy, as it is difficult to ensure that the sphincter has been adequately divided. The accompanying haemorrhage and post-operative bleeding may contribute to the problems. Infection should be treated vigorously with pre-operative and per-operative antibiotic prophylaxis to avoid the risk of septicaemia. Erectile dysfunction appears to be uncommon when anteromedian sphincterotomy is used (Carrion *et al.*, 1979).

The success of the Wallstent in the treatment of urethral strictures (Milroy *et al.*, 1988, 1989) has been due to the successful "holding open" of the strictured area so that epithelialisation can take place. If a relatively unyielding scarred urethra can be held open by a stent, the expansile external sphincter mechanism should also be held open by the same means. It was this principle that led to the use of the external sphincter stent in the present series. Other advantages were ease of placement, absence of haemorrhage, improbability of erectile

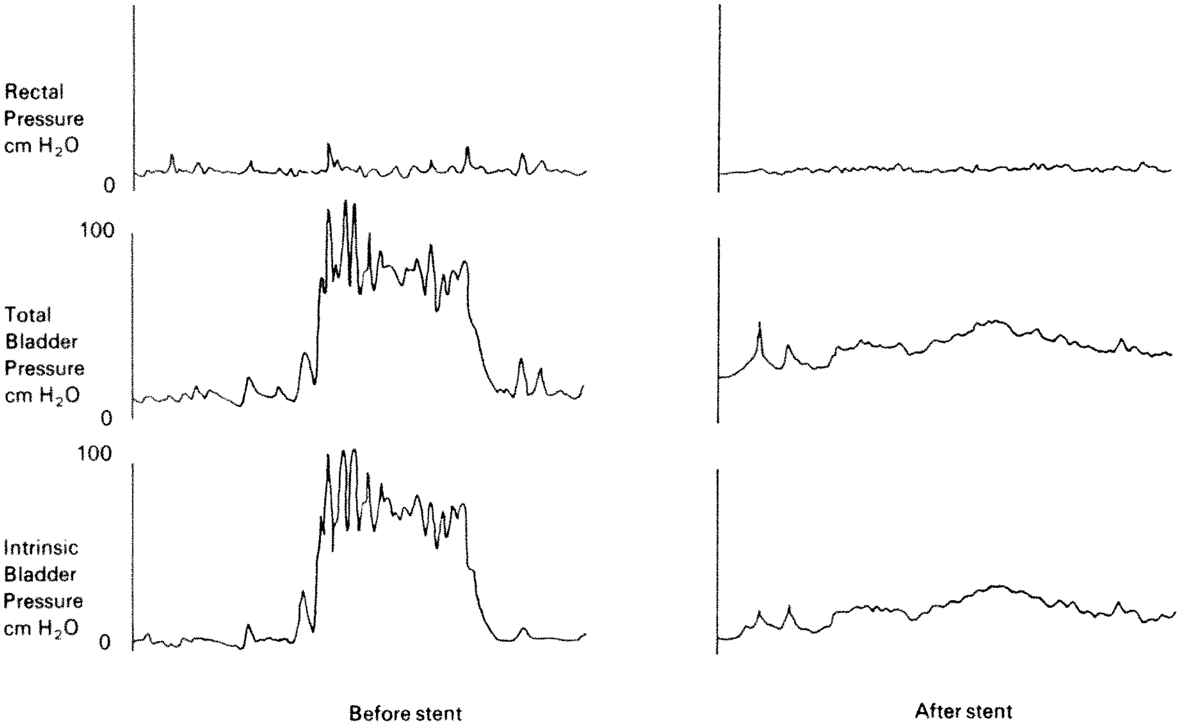

Fig. 3 Urodynamic traces before and after stent insertion demonstrating a reduction in hyper-reflexic voiding pressure and duration of contraction time after stent insertion.

dysfunction and, provided adequate antibiotic prophylaxis is used, the absence of infective complications. The stent can be placed through the external sphincter without difficulty and the 3 cm stent appears to be completely satisfactory in the majority of patients. The lower limit of the apex of the verumontanum is the proximal landmark for placement of the stent.

Endoscopy has been performed in 4 patients at varying times post-operatively. The stent rapidly becomes covered by epithelium (within 2–3 months) as described in urethral stricture patients (Milroy *et al.* 1989). The ends of the stents remain visible for a longer period before becoming covered in epithelium.

Apart from the 1 infective complication, no other problems were encountered. The use of a "prophylactic" suprapubic catheter may not be necessary for more than a week or so once bladder emptying is satisfactory. The suprapubic catheter was useful in assessing bladder emptying and in performing repeat urodynamic studies as an objective assessment of the improvement in urodynamic parameters which was seen in all of our patients. Complete bladder emptying has not occurred in all cases, although the length of follow-up is short. The absolute value for residual urine may not be very important provided bladder emptying is achieved with acceptable pressure and the residual urine is neither infected nor retained under pressure due to

Table Results of Urodynamic Investigations in 9 Patients Before and After Insertion of External Sphincter Wallstent (mean + 1 SD)

	Before stenting	*After stenting*
Bladder volume (ml)	397 ± pm240	248 ± 88
Detrusor pressure (cm H_2O)	94 ± 18	78 ± 15
Duration of contraction (s)	130 ± 88	17 ± 14
Voided volume (ml)	128 ± 123	150 ± 81
Residual urine (ml)	268 ± 219	92 ± 106

Statistically significant differences were seen in the duration of detrusor contraction only (paired *t* test).

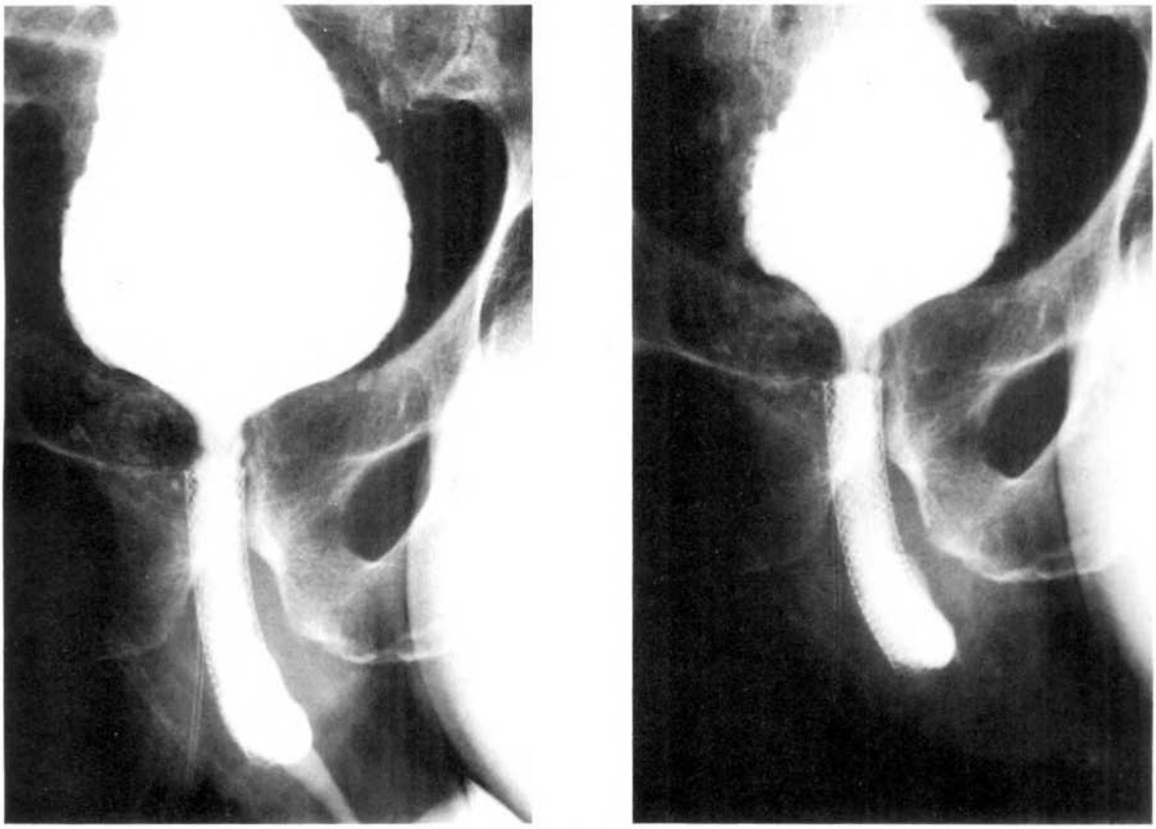

Fig. 4 Radiograph during videourodynamics after stent insertion demonstrating a wide open external striated sphincter.

poor bladder compliance. It is hoped that the long-term results of external sphincter stenting will match the early encouraging results. Provided problems do not develop with the wire of the stent (fragmentation of the wire has been suggested), permanent stenting should be trouble-free. Ulceration and para-urethral abscess have been suggested as potential complications, but we have not encountered them. If the stent is to be removed for any reason this could be technically very difficult once permanent incorporation is complete.

The following recommendations for stent insertion in spinal injured patients should be considered.

(1) Patients should be quadriplegic and should be candidates for external striated sphincterotomy and condom drainage. They should be over the age of 30 years.

(2) Videourodynamic studies and urinary tract ultrasound should be performed prior to stent insertion.

(3) Urinary tract infection must be adequately treated and per-operative antibiotics given.

(4) Ascending urethrography is necessary only if a urethral stricture is suspected.

(5) Suprapubic catheterisation prior to stent insertion is recommended. The catheter may be removed as soon as complete bladder emptying is shown by the measurement of residual urine. The catheter is also useful for filling cystometry to assess the efficacy of treatment.

Acknowledgements

We thank Mr I. B. Bayley, Director, and Dr F. Middleton, Consultant in Rehabilitation Medicine, and the nursing staff of the Spinal Injuries Unit for their help and co-operation in introducing this new technique and for helping in the management of the patients.

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The Authors

P J R. Shaw, FRCS, Senior Lecturer, Institute of Urology, Honorary Consultant Urologist, St Peter's Hospitals, London, Consultant Urologist, Spinal Injuries Unit, Royal National Orthopaedic Hospital.

A G Timoney, FRCSI, Lecturer in Urology, Institute of Urology and Spinal Injuries Unit, Royal National Orthopaedic Hospital

E J. G. Milroy, FRCS, Consultant Urologist, Middlesex Hospital, London.

A Eldin, MD, Medical Adviser, Medinvent SA, Lausanne, Switzerland

Nan Mitchell, Consultant Radiologist, Royal National Orthopaedic Hospital

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Symptoms versus Flow Rates versus Urodynamics in the Selection of Patients for Prostatectomy

J. McLOUGHLIN, K. P. GILL, P. D. ABEL and GORDON WILLIAMS

Department of Surgery, Royal Postgraduate Medical School, Hammersmith Hospital, London

Summary—Many prostatectomies are performed on the basis of symptoms alone; 39% of patients referred by their family doctors and 23% of patients who were on waiting lists for prostatectomy of other hospitals, but who had not undergone any urodynamic investigations, were found to be unobstructed on urodynamic criteria. A screening peak urinary flow rate of 12 ml/s or less was associated with urodynamic evidence of obstruction in 95% of cases; 35% of patients with symptoms of outflow obstruction and a flow rate > 12 ml/s were also found to be obstructed.

One year post-operatively, 84% of patients who were selected for surgery on combined symptomatic and urodynamic criteria were pleased symptomatically with their result. The failure of detrusor instability to resolve following prostatectomy was associated with symptomatic failure of treatment. Residual obstruction was demonstrated in 5 patients who had undergone prostatectomy and were asymptomatic at this time.

This study illustrates that objective measures are necessary in the assessment of patients prior to prostatectomy in order to select only patients who are obstructed. The importance of a screening flow rate is emphasised. All patients who underwent surgery had cystometric evidence of obstruction but the symptomatic results of surgery were no better than the results in patients who had been assessed according to non-urodynamic selection criteria. We have thus failed to identify a need for routine cystometry in the pre-operative assessment of these patients. Cystometry does, however, have a role in assessing patients with pre-operative flow rates > 12 ml/s and in those who remain symptomatic following prostatectomy.

The lack of appropriate equipment means that many surgeons and even some urologists must select patients for prostatectomy on the basis of symptoms and clinical examination alone. Symptoms are often unreliable (Andersen *et al.*, 1979) and the only ones that have been reliably associated with outflow obstruction are hesitancy and poor stream (Abrams and Feneley, 1978). A poor urinary stream, however, may result from impaired detrusor contractility and hesitancy may result from bladder instability without obstruction (Blaivas, 1988). The symptoms of frequency, nocturia and urgency are often those that the patients find most distressing but these may be due to bladder instability in the absence of obstruction (Turner Warwick *et al.*, 1973). It is therefore important to confirm that genuine obstruction is the cause of the patient's symptoms, since unnecessary surgery may otherwise be undertaken.

We carried out a symptomatic and objective assessment of men who were referred for prostatectomy and report the influence of these investigations on the results following surgery.

Patients and Methods

The series included 108 men; 39 were referred by family doctors with symptoms of bladder outflow obstruction and 69 were already on various hospital waiting lists for prostatectomy but had not undergone a urinary flow rate or urodynamic assessment. A standardised proforma was used to record daytime and nocturnal frequency of micturition, urgency, incontinence, degree of hesitancy, strain-

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ing and the subjective sensation of bladder emptying. Peak urinary flow rate was then measured using a capacitance flow meter (Micromedics, Ltd, System One VI. 4), followed by evaluation using a Lectromed (MX6 × 6) multichannel recorder connected to urethral and rectal solid state pressure transducers (Gaeltec). Medium fill cystometry (Abrams *et al.*, 1983) was performed through a 12 F urethral catheter with saline warmed to room temperature. Filling was undertaken with the patient sitting and he was asked to cough and strain in an attempt to provoke detrusor instability. He voided in the standing position following removal of the filling catheter but with the pressure lines still *in situ*. A urethral resistance factor (R) was calculated from the detrusor pressure (P det) at maximum flow (Q max) where $R = P\ det/(Q\ max)^2$. A value of $R \geqslant 0.5$ was used to define obstruction (Coolsaet and Blok, 1986). Detrusor instability was defined as an autonomous rise in detrusor pressure > 15 cm of water (I.C.S., 1976).

One year after prostatectomy all patients were invited to attend for a repeat flow rate and symptomatic assessment. Patients with residual symptoms or peak flow rates < 12 ml/s were offered repeat urodynamic investigation.

Results

All patients had symptoms suggestive of bladder outflow obstruction. Using cystometry, 24 of the 39 family doctor referrals (61%) and 53 of the 69 patients (77%) on hospital waiting lists for prostatic surgery were obstructed; 31 patients (28%) had symptoms associated with bladder outflow obstruction but were unobstructed on urodynamic criteria (16 had detrusor instability, 12 had normal cystometrograms and 3 had low flow rates due to impaired detrusor contractility as defined by Blaivas (1988).

Using a peak flow rate ≤ 12 ml/s as an index of obstruction, 65 patients (60%) were identified. A flow rate alone was accurate in 95% of cases, with 62 patients being obstructed on urodynamic evaluation; 43/108 patients (40%) had flow rates > 12 ml/s and 15 of these (35%) were obstructed; 52 (68%) of the 77 patients with and 14 (45%) of the 31 without evidence of outflow obstruction had detrusor instability at the time of initial presentation.

Of 53 patients with outflow obstruction as defined by cystometry who agreed to undergo TURP, 37 (69%) returned 1 year later for a repeat free flow rate and symptomatic assessment. The flow rates of 3 men were excluded because of low voided volumes (< 150 ml). Of the 34 patients voiding more than 150 ml, 27 (79%) had improved flow rates compared with those recorded pre-operatively, 25 (74%) had peak flow rates > 12 ml/s and 9 (26%) had peak flow rates ≤ 12 ml/s.

Of the 9 patients with flow rates < 12 ml/s at 1 year, all were satisfied with the symptomatic results of surgery, although only 6 had an improved flow rate. Cystometry showed that 5 were obstructed and 2 were unobstructed; 2 refused repeat cystometry. None of the 7 patients who agreed to undergo cystometry had detrusor instability.

Of the 37 patients, 31 (84%) were symptomatically pleased with the results from a urinary point of view (1 patient complained of loss of libido which he blamed on the operation and is therefore not included in the above calculations); 6 (16%) felt that the operation had not been a success and they had persistent urinary symptoms. Of these 6 patients, 2 had normal cystometry and 4 had detrusor instability (3 without evidence of residual obstruction and 1 with obstruction) which had failed to resolve following surgery. One of the patients with instability also had a degree of stress incontinence. No patient with residual symptoms had a flow rate < 12 ml/s at follow-up. None of the patients with initially higher flow rates who underwent TURP were noted to have residual symptoms at follow-up. All patients in this group had improved flow rates compared with pre-operative measurements.

Discussion

Men presenting with hesitancy, poor flow, frequency and nocturia are usually assumed to have bladder outflow obstruction and are expected to benefit from prostatectomy. Owing to lack of formal training or an absence of suitable equipment for the diagnosis of this condition, many surgeons select patients for prostatic surgery on the basis of symptoms alone.

We studied 108 patients with symptoms of bladder outflow obstruction. Only 61% of family doctor referrals and 77% of those already on hospital waiting lists (who had been assessed on the basis of symptoms alone) were considered obstructed following cystometry. Failure to carry out any type of urodynamic assessment would have resulted in 23% of the patients already on waiting lists undergoing unnecessary surgery.

An initial free flow rate ≤ 12 ml/s was associated with bladder outflow obstruction as defined by cystometry in 95% of patients and this should be considered the minimum investigation required in the selection of patients for surgery. Guided only by a free flow rate ⩽12 ml/s as an indicator of obstruction, only 3 patients (3%) who were subsequently found to have impaired detrusor contractility would have been unnecessarily subjected to TURP. Blaivas (1988) highlighted the pitfalls of relying solely on the free flow rate as an indication of obstruction and stressed the need for pre-operative pressure flow studies. A major difficulty in using such investigations remains the definition of obstruction. A urethral resistance factor, as used in our study, to indicate obstruction is based on rigid tube hydrodynamics and has been criticised especially where detrusor pressure/flow rate ratios are equivocal (International Continence Society, 1980). A "dynamic urethral resistance relation" (DURR) and a "passive urethral resistance relation" (PURR) have been suggested as better indicators of true lower urinary tract function (Schafer *et al.*, 1981) but have only a limited role in routine clinical practice (Coolsaet and Blok, 1986).

Of the 37 patients who returned 1 year after prostatectomy and underwent symptomatic and urodynamic assessment, 6 (16%) had residual urinary symptoms. Three of these patients had persistent detrusor instability and 1 remained both obstructed and unstable. This observation, that the non-resolution of instability secondary to outflow obstruction following prostatectomy is associated with symptomatic treatment failure, has been described by Abrams *et al.* (1979) and Kadow *et al.* (1988). It is of note that all 9 patients with flow rates <12 ml/s were happy with the results of surgery, yet only 6 of these had an improved flow rate. Of those who agreed to undergo cystometry, 5 were still obstructed (2 refused cystometry and 2 were unobstructed) and 7 were stable. This suggests that residual obstruction following surgery is not associated with a failure to obtain symptomatic relief unless instability resulting from the obstruction also fails to resolve. This also illustrates that when objective means of determining results following prostatectomy are employed, the incidence of obstruction is higher than would be expected on the basis of a patient's symptoms alone.

Previous studies have demonstrated that 86% (Abrams, 1977) of patients improved symptomatically following prostatectomy when selected on the basis of symptoms alone. In the present study, using a combination of symptomatic and urodynamic criteria, 84% showed symptomatic improvement; Abrams *et al.* (1979), using similar criteria, observed symptomatic improvement in 88%. On the basis of these results it is difficult to advocate routine urodynamic investigations in patients presenting with symptoms suggestive of bladder outflow obstruction other than a free flow rate, which is simple to perform and 95% accurate. Where cystometry does have a role is in patients with a free flow rate >12 ml/s and typical symptoms, and also in the assessment of patients with persistent symptoms following surgery. The value of a free flow rate to measure improvement after prostatectomy should also be emphasised.

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The Authors

J McLoughlin, FRCS, Urology Registrar.

K. P. Gill, FRCSI, Urology Registrar.

P. D. Abel, ChM, FRCS, Senior Lecturer and Honorary Consultant in Urology.

Gordon Williams, MS, FRCS, Consultant Urologist.

Requests for reprints to: Gordon Williams, Department of Surgery, Hammersmith Hospital, Du Cane Road, London W12 0HS

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Pathological Classification and Follow-up of Prostatic Lesions Initially Diagnosed as "Suspicious of Malignancy"

P. F. KEANE, I. C. ILESLEY, E. P. N. O'DONOGHUE and M. C. PARKINSON

St Peter's Hospitals, London

Summary—Sections from a series of prostatic specimens ($n=44$) in which the initial diagnosis implied a suspicion of malignancy were reviewed and the patients followed up (group 1). The aim was to categorise the morphological appearances according to current criteria and to determine the natural history of any pre-malignant lesions within this group. A "control" series of patients ($n=40$) in whom the primary diagnosis was benign were also reviewed and their course followed (group 2).

The heterogeneity of the abnormalities in group 1 was striking. Of the 44 cases, pre-malignant lesions were seen in 8, microinvasive adenocarcinoma in 11 and lesions not now considered pre-malignant in the remaining 25. None of the 8 patients with pre-malignant lesions developed clinical evidence of carcinoma over a follow-up period of 8 to 12 years. In contrast, 3 of the 11 diagnosed on review as having microscopic invasive adenocarcinoma developed clinically evident tumour within 5 years of surgery. Of the 25 patients whose prostatic lesions were considered benign, 2 developed carcinoma 12 and 13 years after surgery. Only 1 of the 40 patients in group 2 had a pre-malignant lesion and he did not develop tumour within 10 years. However, adenocarcinoma was diagnosed incidentally in 1 patient 3 years after surgery.

It was concluded that there is a need to standardise interpretation and reporting of pre-malignant lesions and microscopic foci of adenocarcinoma in the prostate. The limited results on the course of pre-malignant lesions diagnosed incidentally in patients over 60 years of age do not indicate that follow-up would have prompted the early diagnosis of invasive disease.

Adenocarcinoma is a frequent cause of morbidity in men over 60 years of age and is the third commonest cancer in males with approximately 8000 new cases diagnosed each year. In 1987, 7166 deaths were recorded in England and Wales from carcinoma of the prostate (Office of Population Censuses and Surveys, 1987). Despite these facts and in contrast with carcinoma at other sites, little is known of the pre-invasive lesion and its course in the prostate.

A number of possible pre-invasive malignant epithelial lesions have been described under various names. The diagnostic criteria for the categories used have not always been precisely stated and equivalence therefore is difficult to establish. With this reservation, 2 major groups of pre-malignant lesions have been described in literature reviews (Bostwick, 1988; Miller 1988).

1. Those depending on cytological features of malignancy in acini or ducts which show a normal microanatomy and are composed of a double or stratified layer of cells. These features are similar to the intraepithelial neoplasia or dysplasia described in other sites.
2. An architectural abnormality characterised by proliferation within a lobule of closely packed small regular glands with circular lumina (devoid of the epithelial infoldings normally seen). The glands are composed of a double or single layer of cells, the inner layer being cuboidal and commonly showing clear cytoplasm. Cytological

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abnormalities and an invasive growth pattern are absent.

These morphological features are seen more commonly in malignant than benign glands, so that when they are diagnosed in surgical or biopsy specimens in the absence of carcinoma the search for a concurrent tumour is indicated. In contrast, there is little information regarding the relationship between the putative pre-malignant lesions and subsequent carcinoma on which the surgeon can base a decision regarding follow-up.

The aims of this retrospective study were to apply currently defined morphological criteria for the diagnosis of prostatic pre-malignancy and to relate these findings to the subsequent course of the prostatic disease.

Patients and Methods

The records of the St Peter's Hospitals histopathology department for the years 1975 to 1979 were examined and all reports on prostatic specimens in which malignancy was suspected but not diagnosed were extracted (group 1). These included diagnoses of "atypical foci", "areas suspicious but not diagnostic of malignancy" and "appearances indicating/suggesting follow-up". Such a report was issued in 110 of the 1256 (8.7%) prostatectomies performed in the 5-year period. At the same time, 120 reports of benign disease were extracted in which no such statements had been made (group 2). All case notes were reviewed and questionnaires sent to the patient's family doctor inquiring about their general health and whether the patient had any further prostatic symptoms or prostatic disease.

Histopathological review was restricted to cases where complete follow-up was achieved—50 and 40 from groups 1 and 2 respectively. Six patients in group 1 were subsequently excluded; in 2 patients the needle biopsy specimen was insufficient for the purposes of this study, in 1 patient prostatic carcinoma had been diagnosed on a previous resection and in 3 patients the material on file available for review was incomplete.

In group 1 the weight of the 39 transurethral resection (TUR) specimens ranged from 3.5 to 33.0 g (average 16.0). The 5 retropubic prostatectomy specimens weighed between 70 and 85 g. In group 2 the weights of the 38 TUR specimens ranged from 1.5 to 64 g (average 16.4). The 2 retropubic specimens weighed 60 and 79 g (average 68.5).

In the years included in this study it had not been the practice to process the entire TUR specimen for histopathological examination in all instances, sampling being related to weight at the discretion of the reporting histopathologist. Where lesions suspicious of malignancy were seen on the initial sections, further samples from the specimen were processed. In group 1 patients the entire specimen had been processed in 16 cases; more than half of the resected tissue was available for examination in 22 instances and in 1 case less than half the weight of the resected prostate had been sampled. In group 2 the entire specimen had been processed in 5 cases, more than half of the resected tissue in 8 cases, and less than half in 25 cases. From retropubic prostatectomies in both groups 1 and 2, solid or cream-coloured areas were selected and otherwise random blocks were taken.

The original sections of all specimens were reviewed on 2 occasions by both histopathologists (I.C.I. and M.C.P.), who were aware of the initial "suspicious" and "benign" diagnoses made in groups 1 and 2 respectively but had no knowledge of the patient's subsequent course. On the initial examination of group 1 the criteria for epithelial dysplasia defined by McNeal and Bostwick (1986) were applied and the diagnosis of architectural atypia was based on reviews by Brawn (1982) and Kovi (1985) (Figs 1 and 2). However, both histopathologists found that they could unanimously, reliably and reproducibly recognise only the severe grade of dysplasia (grade 3), so observa-

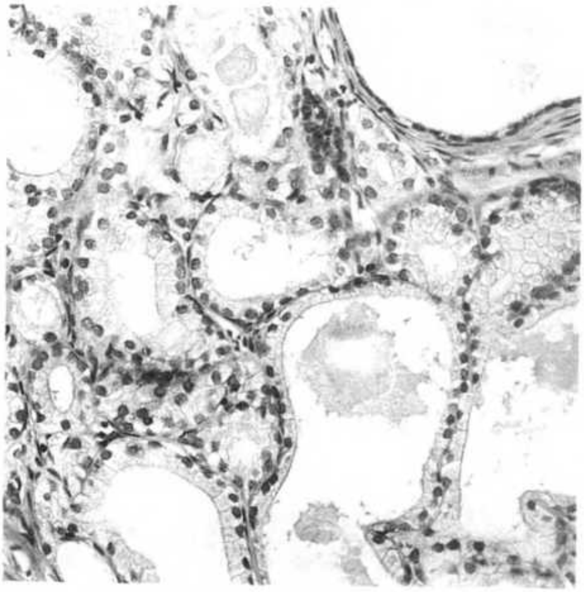

Fig. 1 Crowded glands lined by a single layer of cytologically bland epithelium: atypical adenosis. (H and E × 200).

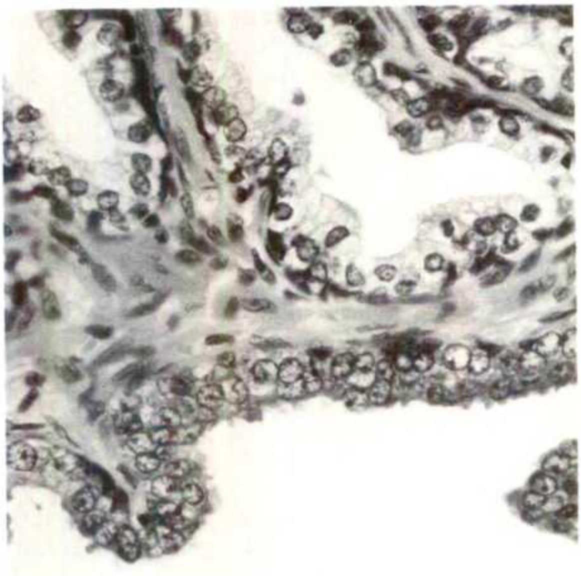

Fig. 2 Glands lined by cytologically atypical epithelium, many of which have prominent nucleoli, but without an infiltrative pattern: dysplasia (H and E × 400).

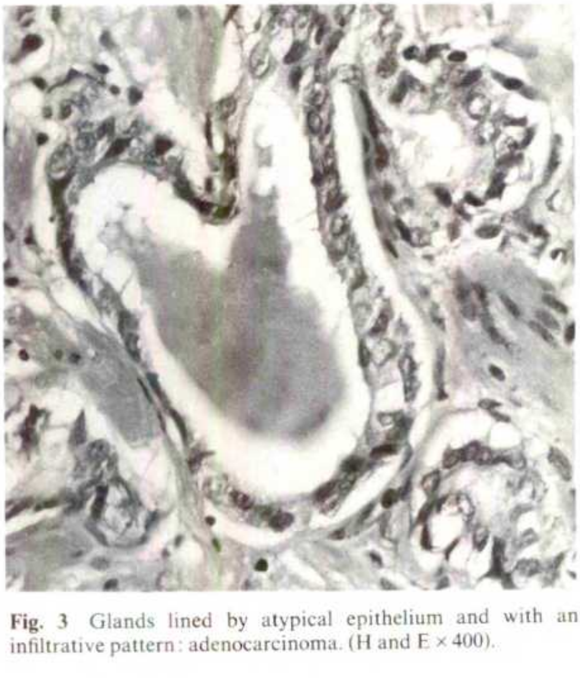

Fig. 3 Glands lined by atypical epithelium and with an infiltrative pattern: adenocarcinoma. (H and E × 400).

tions were limited to this form. The category of architectural atypia was found to be more difficult to apply than that of severe dysplasia. Such lesions were difficult to distinguish from proliferating foci of benign hyperplasia and both observers doubted their reproducibility of this diagnosis.

In addition to the pre-malignant lesions, appearances that would now be interpreted as small foci of frank adenocarcinoma were seen. This diagnosis was based on both an invasive growth pattern and cytological atypicality (Fig. 3).

A third group of morphological appearances was defined which, although not currently considered pre-malignant, had prompted this diagnosis in the period 1975 to 1979: basal cell hyperplasia and cribriform patterns of epithelial hyperplasia without cytological atypia.

Finally, a group remained in which minor abnormalities were seen (including sclerosing adenosis and hyperplastic transitional epithelium lining ducts) which may have caused concern at the initial diagnosis but for the purpose of this study were classified as showing "no significant abnormality". As a result of the first review the following categories emerged:

Small foci of adenocarcinoma	
Pre-malignant lesions	Severe dysplasia. Architectural atypia.
Benign lesions considered in the differential diagnosis of pre-malignancy	Basal cell hyperplasia. Cribriform hyperplasia without atypia.
No significant abnormality	Sclerosing adenosis. Hyperplastic transitional ductal epithelium.

The histopathological review of sections from patients in group 1 was then repeated using these categories. In cases showing foci of carcinoma, dysplasia and architectural atypia, the proportion of fragments so involved was noted.

The histopathology from patients in group 2 was reviewed and evidence of the morphological groupings which had been defined during the study of group 1 cases was recorded.

Results

The age range, presenting symptoms and treatment of the patients in groups 1 and 2 are shown in Table 1. In Group 1, follow-up ranged from 24 to 160 months (median 118) and in Group 2 follow-up ranged from 40 to 156 months (median 125); 29 of 44 patients in Group 1 (66%) are alive and 1 died of prostatic cancer. Two other patients died from cancer in Group 1, the tumours originating in bronchus and stomach. All other deaths in this

Table 1 Clinical Features

	Group 1	*Group 2*
Age (years)		
Range	40–91	48–86
Median	65	63
Presentation		
Outflow obstruction	72	68
Retention	6	16
Infection	10	8
Haematuria	12	8
Treatment		
TURP	88	92
Retropubic prostatectomy	12	8

group were from cardiovascular disease. In Group 2, 30 patients (75%) are alive and all deaths in this group were due to cardiovascular disease.

The relationship between histopathological review diagnosis and clinical course in group 1 patients is shown in Table 2. Eleven patients had microscopic foci of invasive carcinoma not involving more than 5 chips and not exceeding the Gleason sum score of 5. Severe dysplasia was also present in 6 of these specimens and architectural atypia in 3; in 1 of these cases both lesions were present. Three of these patients had evidence of clinically significant carcinoma of the prostate within 5 years of TUR: 1 developed obstructive uropathy and died at 3 years, another was treated by radiotherapy and is alive at 12 years and the third patient has a T3 tumour but is alive at 13 years. Of the remaining 8 patients with focal microscopic carcinoma, 4 died of cardiovascular disease within 5 years and 4 are alive and asymptomatic.

Seven patients had severe epithelial dysplasia and 1 patient had architectural atypia in the absence of carcinoma. None of these patients subsequently developed clinically significant tumour.

Table 2 Histopathological Diagnoses and Clinical Course

	Histological diagnosis No	*Clinical carcinoma*	
		No	*Time (years)*
Microscopic carcinoma	11	3	2 5, 4, 5
Epithelial dysplasia	7	0	
Architectural atypia	1	0	
Basal cell hyperplasia	9	1	13
Cribriform hyperplasia	7	1	12
No significant abnormality	9	0	

Of 25 patients with lesions that are not now considered malignant or pre-malignant, 2 developed carcinoma 12 and 13 years respectively after prostatic surgery.

On review of the histopathology from group 2 patients, focal carcinoma was not seen. A pre-malignant lesion (severe dysplasia) was present in only 1 patient who is alive and asymptomatic at 10 years.

In 1 of the patients a focal adenocarcinoma was diagnosed on a second transurethral resection 3 years after initial surgery and he died from a ruptured aneurysm without developing further prostatic symptoms 3 years later.

Discussion

Carcinoma of the prostate is the third commonest malignancy in men (Office of Population Censuses and Surveys, 1987). Little impact has been made on the frequency with which it causes death, as 75% of patients in the United Kingdom present with T2, T3 and T4 tumours (Chisholm, 1985), of whom more than half have metastatic disease. Therefore efforts are concentrated on the detection of early stage disease which may be cured by radical surgery or radiotherapy. In this context attention has also returned to the definition and course of pre-malignant lesions of the prostate.

In the majority of investigations the *concomitant* relationship between such lesions and carcinoma has been demonstrated. One of the aims of this study was to investigate the course of pre-malignant lesions to see if a *sequential* relationship could be established between these morphological changes and subsequent prostatic malignancy. Thus a series of cases in which the presence of pre-malignant lesions had been suggested and "controls" in which a benign diagnosis had been made were reviewed, the morphological features categorised according to recent criteria and patients followed up.

In the literature a variety of lesions have been defined to which a pre-malignant nature has been ascribed. It is not always possible to establish clear equivalence between the lesions described by different pathologists but 2 major morphological types can be distinguished. In one the diagnosis is dependent on atypical cytological features with a normal or hyperplastic duct/acinar architecture and in the other the predominant abnormality is the acinar growth pattern resulting in anomalous microanatomy. Oyasu *et al.* (1986), Billis (1986) and McNeal (1988) gave similar descriptions of cytological pre-malignancy for which McNeal used the term "dysplasia" or "prostatic intra-epithelial neoplasia" (McNeal and Bostwick, 1986). Brawn (1982) was the major proponent of the pre-malignant nature of architectural anomalies but cytological atypia was included in his description (Brawn *et al.*, 1989). The forms of pre-malignancy defined by Kastendieck (1980) and Helpap (1980) were summations of both cytological and architectural features.

The evidence for the pre-malignant nature of the above lesions is the morphological similarity to carcinoma, continuity with or proximity to the tumour (Kastendieck, 1980; Oyasu *et al.*, 1986), a similar distribution to cancer in the posterior part of the gland (Billis, 1986) and the more frequent occurrence in malignant than in benign glands (Helpap, 1980). Additional indicators of a pre-malignant nature include the autoradiographic demonstration of a labelling index higher than hyperplasia and similar to carcinoma (Helpap, 1980), the increasing disruption of the basal layer with increasing grades of dysplasia (Bostwick and Brawer, 1987) and the loss of differentiation markers (McNeal *et al.*, 1988).

We elected to review the current series in terms of cytological evidence of atypia (dysplasia) and architectural abnormalities as described in reviews by Bostwick (1988) and Miller (1988). Our pathologists agreed on the diagnosis of severe dysplasia but on less marked changes results were inconsistent. The category of architectural atypia was found to be more difficult to apply than that of severe dysplasia. The lesions were difficult to distinguish from proliferative areas in benign hyperplasia and the diagnosis could not be reliably reproduced. It was therefore felt that the reporting of architectural atypia was of questionable value. Gleason (1985) also expressed the view that "adenosis" as defined by Brawn (1982) may include examples of adenocarcinoma Gleason 1+2.

One of the most important results of this review has been to draw attention to the variety of morphological appearances which induce a guarded diagnosis with respect to malignancy. In 25 of the 44 specimens in group 1, pre-malignant and malignant foci were not apparent according to current criteria. In this respect one of the major diagnostic hazards proved to be basal cell hyperplasia. This diagnosis and other lesions causing confusion with pre-malignancy have been discussed by Bostwick (1988). In 11 specimens, foci of invasive adenocarcinoma were present as judged by an infiltrative pattern. The diagnostic difficulties involved in distinguishing small foci of well differentiated adenocarcinoma from possible pre-malignant architectural atypia have been discussed by Gleason (1985) and Srigley (1988).

Eight of these 11 cases were also the site of pre-malignant lesions and an additional 8 contained such lesions in the absence of carcinoma. Pre-malignant changes were diagnosed in only 1 of the 40 patients (group 2) in whom the initial findings were of benign disease.

Follow-up revealed that 3 of the 11 patients (27%) with foci of adenocarcinoma on review developed clinical evidence of invasive disease within 5 years of surgery. In the summated 64 patients (groups 1 and 2) with benign disease on review, 3 (4%) developed carcinoma 3, 12 and 13 years after surgery. These findings are similar to those of other workers who reported progressive carcinoma in 4 of 15 and 8 of 50 patients with stage AI carcinoma in intervals varying from 7 to 11.5 years (Blute *et al.*, 1986; Epstein *et al.*, 1986). Of the 9 patients (summation of groups 1 and 2) with pre-malignant lesions in the absence of carcinoma, none developed clinical cancer in a follow-up period ranging from 8 to 12 years.

We conclude that the histopathological lesions previously indicated as pre-malignant are heterogeneous and that there is a need for histopathologists to establish uniform criteria, interpretation and nomenclature. This is particularly necessary for small foci of adenocarcinoma.

It seems most likely that the original reporting histopathologists recognised these lesions as carcinoma but did not report them as such. At the time of initial diagnosis there was a reluctance to report occasional small foci of adenocarcinoma for fear the patient might be subjected to controversial radical therapy. Thus a variety of euphemisms were substituted for a frankly malignant diagnosis. This approach probably resulted from the opinion that small incidental areas of carcinoma were examples of latent tumour which was said not to progress. On closer examination the concept of latent disease is based on necropsy studies which did not include a detailed search for lymph node metastases (Edwards *et al.*, 1953; Franks, 1954). Current findings relate metastatic potential to the size of the primary lesion (McNeal *et al.*, 1986) rather than an inherent biological difference in the neoplasm. It may be that treatment of small foci of carcinoma which causes progressive clinical cancer in 27% in a population with a 30% mortality rate from cardiovascular disease within the same period may not be justified. However, ultrasound examination with biopsy and/or "second look" TURP should be considered in younger patients. In addition, accurate reporting will enable the course of pre-malignant lesions to be assessed independently of small foci of adenocarcinoma.

In the 9 patients with pre-malignant lesions (summated groups 1 and 2) in the absence of carcinoma there was no evidence of clinical tumour over a period ranging from 8 to 12 years.

These findings do not indicate that a follow-up of patients exceeding 60 years of age with pre-malignant lesions diagnosed incidentally would prompt early diagnosis of invasive cancer during their expected life span. However, our own peripheral finding in this series, in common with other larger studies, has shown a concomitant correlation between lesions described as pre-malignant and invasive carcinoma. Eight of the 17 prostates in which pre-malignant lesions were found on review (summation of groups 1 and 2) also contained foci of adenocarcinoma. Thus the former diagnosis should prompt a detailed search of the tissues available for malignant tumour. The latter association is particularly important in patients undergoing biopsy or TUR for clinically suspected or ultrasound evidence of carcinoma. The finding of severe dysplasia in such patients should prompt consideration of further biopsy.

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The Authors

P F Keane, MCh, FRCSI, Lecturer in Urology, St Peter's Hospitals/Institute of Urology

I. C. Ilesley, MRCPath, Senior Registrar, Bloomsbury District Histopathology Department.

E. P N O'Donoghue, FRCS, Consultant Urologist, St Peter's Hospitals.

M. C. Parkinson, BSc, MD, FRCPath, Consultant Histopathologist/Senior Lecturer, St Peter's Hospitals/Institute of Urology.

Requests for reprints to· P. F. Keane, Department of Urology, Hammersmith Hospital, Du Cane Road, London W12 0HS.

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Granulomatous Orchitis

Review of 15 Cases

M. AITCHISON, G. R. MUFTI, J. FARRELL, P. J. PATERSON and R. SCOTT

Department of Urology, Royal Infirmary, Glasgow

Summary—Granulomatous orchitis is a rare lesion of the testis which can clinically simulate malignancy. The clinical, radiological and pathological features of 15 patients are presented and discussed.

Granulomatous orchitis is a chronic inflammatory lesion of uncertain aetiology (Morgan, 1976). From the clinical point of view it is important because it presents as a swelling of the testis which closely simulates malignancy. It is a rare condition and less than 100 cases have been reported in the Western literature. Apart from 2 series published more than a decade ago, the literature includes only sporadic case reports (Capers, 1962; Lynch *et al.*, 1968; Morgan, 1976; Heyderman *et al.*, 1988). The rare nature of this condition prompted us to undertake a clinical and pathological review of our experience over the past 10 years.

Patients and Methods

The pathological files of 2 institutions (Royal Infirmary and Western Infirmary, Glasgow) were reviewed over the period 1978 to 1988. The clinical and pathological data of all patients who had undergone orchiectomy for inflammatory conditions were studied. The study group comprised 15 patients in whom the pathological features were consistent with a diagnosis of granulomatous orchitis.

Results

The patients' mean age was 54 years (range 21–76) with 11 of the 15 being in their fifth decade. All presented with scrotal discomfort varying in intensity from a dull ache to severe pain; 13 patients had noted an associated testicular swelling. The right testis was involved in 7 patients and the left in 8; in no case was the disease bilateral.

Six patients had associated urinary symptoms of frequency of micturition, dysuria or nocturia. One patient complained of influenza-type symptoms with transient myalgia and lethargy. One patient had undergone plication of a hydrocele on the affected side 10 years previously.

Urine culture demonstrated a positive growth of *Escherichia coli* in only 2 patients. Six patients had a moderate leucocytosis ($7.0–10 \times 10^9/l$); the remainder had a normal white cell count. The serum oncofetal antigens, alpha-fetoprotein and human chorionic gonadotrophin were below detectable levels in all cases. Ultrasound examination of the affected testis revealed a characteristic pattern of a partially cystic hypo-echoic mass. The radiologist interpreted this as highly suggestive of neoplasm, although a resolving orchitis was listed as part of the differential diagnosis (Fig. 1).

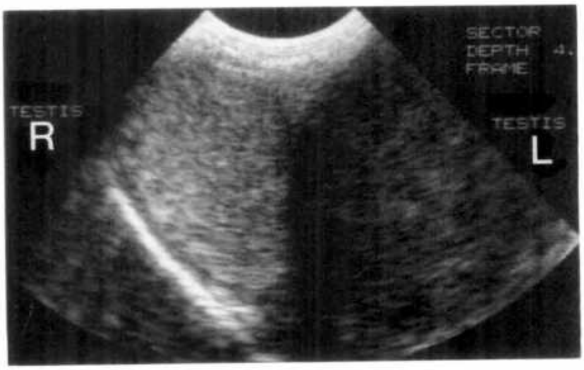

Fig. 1 Ultrasound examination of testes. Left testis is affected by granulomatous orchitis and shows areas of hypoechogenicity.

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In 11 cases, treatment with antibiotics had been instituted by the primary health care physician (with no resolution of the testicular swelling or pain) prior to referral for urological opinion. In all cases the clinical and ultrasonographic findings were thought to be highly suggestive of malignancy and the testis was explored via an inguinal approach. Thirteen patients underwent orchiectomy and in 11 of these the testis was judged on macroscopic examination to harbour a germ cell tumour. In the other 2 cases a frozen section biopsy was undertaken and reported as granulomatous orchitis; the affected testis was felt to be diffusely and irreversibly damaged by the inflammatory process and was therefore excised.

In the remaining 2 patients an open biopsy without excision of the testis was performed but they continued to have testicular pain and swelling for 12 months after exploration. The pain and swelling settled after this period, but subsequent atrophy of the affected testis was noted on clinical examination.

The microscopic features of chronic inflammation in the interstitium in combination with destruction of the spermatogenic cells in the seminiferous tubules were present in all cases. The inflammatory infiltrate consisted predominantly of lymphocytes and plasma cells; neutrophil leucocytes were absent. Eosinophils were identified in 7 of the 15 cases. In the more established cases the seminiferous tubules were present as faint outlines, the lumen being filled by proliferating Sertoli cells. In 3 cases giant cells were present (Fig. 2). No spermatozoa were demonstrated in the interstitium. In 5 cases there was evidence of chronic inflammation in the epididymis and in 3 a sperm granuloma in this site was identified. Ziehl-Nielson stains did not reveal the presence of alcohol/acid fast bacilli. No viable testicular tissue was identified in any of the specimens.

Discussion

This study has confirmed that granulomatous orchitis is predominantly a disease of the fifth decade, although it can occur at any age after puberty (Lynch *et al.*, 1968; Morgan, 1976). The aetiology remains obscure. The presence of breakdown products of spermatozoa in the granulomata and the sperm antibodies in the serum have led to the hypothesis that an autoimmune process secondary to extravasation of sperms into the interstitium may be responsible. However, these findings may reflect the effects rather than the cause of the disease process (Cruickshank and Stuart-Smith, 1959; Phillips, 1961). In this series, intact spermatozoa could not be identified in the interstitium in any of the specimens.

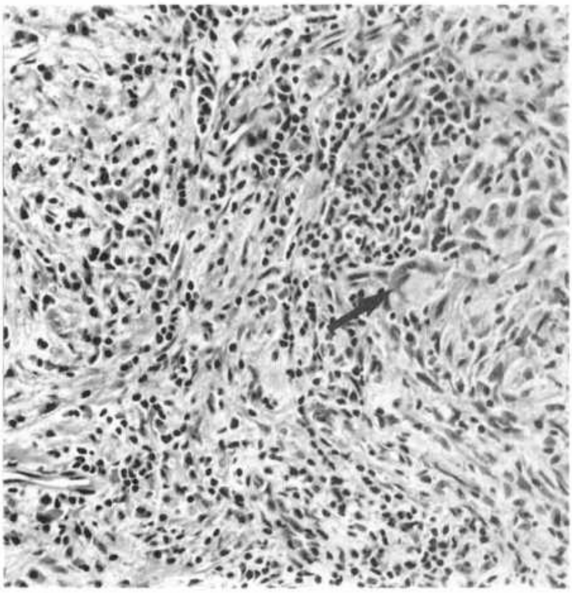

Fig. 2 Granulomatous orchitis with chronic inflammation and destruction of seminiferous tubules. Arrow indicates a giant cell. (H and E × 280).

The presence of associated urinary symptoms in 7 patients raises the possibility of an infective aetiology, although urinary tract infection was documented in only 2 cases. The latter finding may be fallacious, since 11 patients had been treated with antibiotics before referral. This observation, however, highlights the fact that antibiotics have little effect on the course of the disease.

Granulomatous orchitis is a distinct disease entity which should not be confused with granulomatous disease of the testis caused by specific agents or with non-specific epididymo-orchitis (Kahn and McCanirish, 1980). The histological features of chronic inflammation with granulomata in the interstitium and destruction of spermatogenic cells in the seminiferous tubules are characteristic of this condition.

In the last decade, ultrasound has been increasingly used in the diagnosis of doubtful testicular lesions (Howe *et al.*, 1988). This series demonstrates that it is of little value in differentiating granulomatous orchitis from a testicular neoplasm. Although frozen section biopsy can be useful in establishing a peri-operative diagnosis, the complete destruction of seminiferous tubules so typical of this disease justifies orchiectomy as the best treatment, provided that the other testis is normal. This conclusion is supported by the finding that 2 patients in whom biopsy alone was performed continued to have testicular pain and swelling with resultant testicular atrophy.

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The Authors

M. Aitchison, FRCS, Registrar.
G R Mufti, MS, MCh, FRCSE, Consultant Urologist
J Farrell, MB, ChB, Senior House Officer.
P J. Paterson, FRCS, Consultant Urologist.
R. Scott, MD, FRCS, Consultant Urologist.

Requests for reprints to: M. Aitchison, Department of Urology, Glasgow Royal Infirmary, Glasgow G4 0SF.

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Serum Follicle Stimulating Hormone—Predictor of Cancer in the Remaining Testis in Patients with Unilateral Testicular Cancer

EVA HOFF WANDERAS, SOPHIE D. FOSSÅ, A. HEILO, ANNA E. STENWIG and N. NORMAN

Departments of Medical Oncology and Radiotherapy, Diagnostic Radiology and Pathology, Norwegian Radium Hospital; Hormone Laboratory, Aker Hospital, Oslo, Norway

Summary—In 10 of 13 patients with unilateral testicular cancer and subsequent invasive cancer or carcinoma *in situ* in the remaining testis, the follicle stimulating hormone (FSH) level was elevated after the first orchiectomy and before further treatment. In only 4 of 26 comparable control patients was the FSH level raised. This may be because elevated serum FSH often reflects disturbances in spermatogenesis and fertility, the latter being a known risk factor for testicular cancer.

An elevated FSH level that occurs after orchiectomy for unilateral testicular cancer and before further treatment identifies patients at high risk of developing a tumour in the remaining testis.

In approximately 5% of all testicular cancer patients, carcinoma *in situ* is found in biopsies of the remaining testis. Von der Maase *et al.* (1986) reported that 50% of their patients developed invasive carcinoma within 5 years. Maldescent, infertility and testicular atrophy have all been identified as risk factors for the development of cancer in the remaining testis (Skakkebæk, 1978; Berthelsen *et al.*, 1982; Skakkebæk *et al.*, 1982).

In the search for more quantifiable high risk factors we considered serum FSH levels measured after orchiectomy and before further treatment in patients with testicular cancer. Elevated levels reflect disturbed spermatogenesis, which is often found in patients with carcinoma *in situ* (Nielsen *et al.*, 1974; Skakkebæk, 1978; Skakkebæk *et al.*, 1982). Thus one would expect to find elevated FSH values most frequently among patients with a second testicular tumour. The aim of the present study was to test this hypothesis.

Patients and Methods

Between 1979 and 1988, approximately 950 patients with newly diagnosed testicular cancer were referred to The Norwegian Radium Hospital. All were questioned about a history of maldescent and infertility problems. Testicular atrophy was to be assessed clinically, but inconsistent recording of this criterion in the patient's case notes led to its exclusion. Ultrasonography of the remaining testis became part of our routine investigations from 1988 onwards and since then the remaining testis has been biopsied if at least 1 of the following criteria was present: history of testicular maldescent, history of infertility, largest testicular diameter <40 mm.

The biopsy was performed under local anaesthesia with an 18 gauge Bioptic Cut needle, yielding a 23-mm cylinder of tissue for histological examination. The biopsy material was fixed in Bouin's fixative.

Examination of serum FSH was performed routinely in new testicular patients from 1985 onwards. Before then, it had been analysed only when patients requested it. The method has been described by Sand and Torjesen (1973) and Torjesen *et al.* (1974). The upper normal limit of serum FSH was 12 u/l. A database has been established consisting of 350 patients with FSH determination after orchiectomy and before further treatment.

Until July 1988, 13/350 patients had either developed a second invasive tumour in the remaining testis or had carcinoma *in situ* in the biopsy

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Table 1 Details of Patients

	Group I (cases)	*Group II (control)*
No. of patients	13	26
Age (years)	28* (18–54)†	27* (18–51)†
Histology		
Seminoma	8	10
Non-seminoma	5	16
Stage		
I	10	18
II	2	7
III	0	0
IV	1	1
HCG < 5 u/l	13	25
> 5 u/l	0	1
Cytotoxic treatment after first ca.		
Chemotherapy	2	8
Radiotherapy	7	11
No cytotoxic treatment	4	7
Observation time from first ca (months)	38.9* (9–127)†	37.7* (9–112)†
Interval between diagnosis of first and second ca. (months)	29* (0–69)†	—

*Median. †Range.

Table 2 Clinical Risk Factors

Risk factor	*No of patients*	
Infertility		
Yes	0	2
No	5	13
Not assessable	8	11
Maldescent		
Yes	1	4
No	12	22

taken from the remaining testis (Group 1) (Table 1). For each of those patients, 2 testicular cancer patients were selected from the database whose date of birth and date of orchiectomy were closest to those of the patient in question. The control group therefore consisted of 26 age-matched patients (Group 2) with unilateral cancer who did not have, or did not develop, cancer in the remaining testis within the same observation time as those in Group 1.

Statistics

The medians of the FSH values for the 2 groups were calculated. The Fisher exact probability test and the Wilcoxon rank test were used for comparison of the results. A P value <0.05 was considered to be statistically significant.

Results

Five patients had a history of maldescent, 1 in the study group and 4 in the control group (Table 2). None of the patients with bilateral testicular cancer reported infertility, but 2 patients in the control group did so. However, in 19 of the 39 patients fertility could not be evaluated properly because none had tried to father a child before the diagnosis of testicular cancer.

Of the 13 patients in case group 1, 10 had elevated FSH levels compared with 4 of the 26 patients in group 2 ($P<0.01$) (Fig.). The median value in group 1 was 14.7 u/l (range 2.9–41.5) and in the control group it was 7.2 u/l (range 1.3–29.6) ($P<0.01$).

Discussion

Both groups were comparable with regard to stage distribution, treatment and HCG levels at the time of FSH analysis. Chemotherapy was used slightly more in the control group. Infertility and maldescent are associated with an increased risk of testicular cancer. In a Danish study, the incidence of carcinoma *in situ* among infertile men was 0.1% (Skakkebæk, 1978). Mostofi (1973) showed that in 3.6% of 2000 testicular cancer patients the tumour had developed in undescended testes. We did not find an increased incidence of these risk factors in the present series. However, fertility problems could not be evaluated in 19 patients because they had not tried to father a child before the diagnosis of testicular cancer. This risk factor is often impossible to assess in patients with unilateral testicular cancer.

Atrophy of the remaining testis is probably another important risk factor, but it could not be evaluated in the present series owing to the lack of consistent objective criteria in patients examined before the introduction of testicular sonography. Increased use of ultrasonography and objective measurement of the remaining testis will, in the future, allow proper evaluation of testicular atrophy.

The present study indicates that serum FSH, analysed after orchiectomy and before further treatment, is another objective parameter in the identification of patients at high risk of developing a tumour in the remaining testis; 77% of patients who developed a second testicular tumour had elevated FSH levels compared with 15% in the

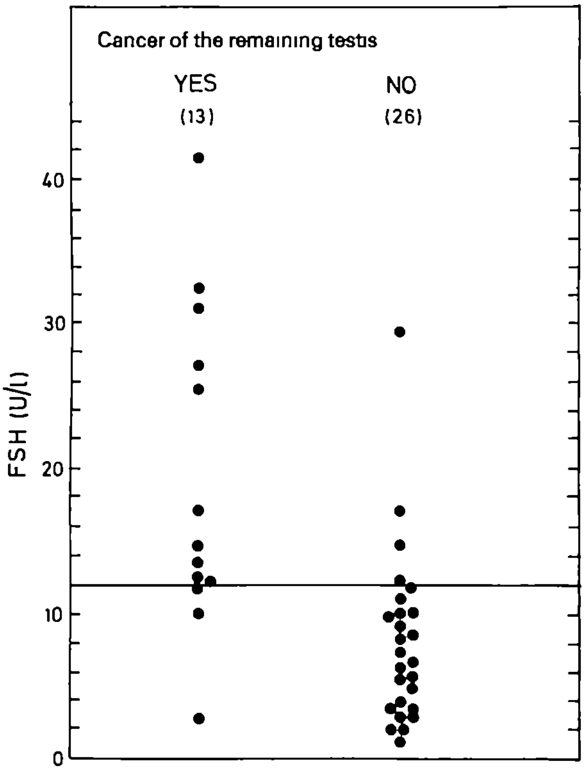

Fig. Serum FSH (analysed after orchiectomy and before further treatment) and cancer in the remaining testis in patients orchiectomised for unilateral testicular cancer
——— Upper limit of normal range.

control group. Why do elevated FSH levels identify these patients? Carcinoma *in situ* of the remaining testis is often combined with severely impaired spermatogenesis (Skakkebæk, 1978), which is associated with elevated serum FSH (Pryor *et al.*, 1976). Severe oligozoospermia or azoospermia may be other factors that indicate an increased risk of subsequent testicular cancer (Horwich *et al.*, 1988). Inadequate information on sperm cell counts in our patients made it impossible to test this hypothesis, but we suggest that reduced spermatogenesis should be evaluated in further studies as a possible risk factor.

In conclusion, an elevated FSH level following orchiectomy for testicular cancer and preceding further treatment identifies patients at risk of developing carcinoma *in situ* or testicular cancer, or those at risk of subsequently developing invasive cancer. These patients should have a testicular biopsy in order to diagnose carcinoma *in situ* at an early stage. Alternatively, they should undergo frequent examination of the remaining testis to diagnose invasive carcinoma as soon as possible.

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The Authors

Eva Hoff Wanderas, MD, Senior Registrar, Department of Medical Oncology and Radiotherapy
Sophie D. Fosså, MD, PhD, Consultant, Specialist in Medical Oncology and Radiotherapy.
A Heilo, MD, Consultant, Specialist in Diagnostic Radiology.
Anna E. Stenwig, MD, Consultant, Specialist in Pathology.
N. Norman, MD, PhD, Consultant, Specialist in Chemical Biochemistry, Hormone Laboratory.

Requests for reprints to. Eva Hoff Wanderas, Department of Oncology and Radiotherapy, The Norwegian Radium Hospital, Montebello, 0310 Oslo 3, Norway.

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Ritual Circumcision (Umkhwetha) amongst the Xhosa of the Ciskei

I. P. CROWLEY and K. M. KESNER

Department of Urology, Cecilia Makiwane Hospital, Mdantsane, Ciskei, South Africa

Summary—The Umkhwetha is an ancient custom of ritual circumcision still practised by the Xhosa people of Southern Africa. In 45 consecutive youths who required hospital admission the mortality rate was 9%. The complications seen over the years are reviewed and their management discussed.

No self-respecting Xhosa girl would marry a Xhosa male unless he had submitted to the Umkhwetha (*um.Kwe-ta*), the Xhosa circumcision ritual for which "boys" are expected to present themselves at between 18 and 22 years of age, although some delay the procedure until later.

The Xhosa people inhabit, in the main, the Ciskei and Transkei areas of Southern Africa. Exact numbers in the Ciskei are currently unknown. The last census was in 1980, when the total population was 630,353 with 178,774 resident in Mdantsane, the town in which this hospital is situated (Preliminary census, 1980).

Patients and Methods

The Umkhwetha takes place twice a year in July and December. In ancient times it was said to have lasted several months. The rite is centred about a specially constructed hut of wattle staves and thatched grass. The circumcision is performed some distance from the hut by the Ingcitsi (surgeon). The boy lies motionless and silent. The Ingcitsi "gloves" the prepuce over his index finger, stretching it with thumb and middle finger. The tissue is rapidly excised with a sharp knife. Residual inner layer tissue is folded back over the distal shaft of the penis. The Izichwe (teacher) then applies specially gathered leaves around the penile shaft. The harmorrhage is staunched by tightly binding the organ with a strip of sheep skin leather. The penis is held obliquely erect by tying the stalks of the leaves to a bark waistband, using another strip of leather.

The would-be man then has his face and body painted white, using a paste made from ground local stone. On his head he wears a garland of mealie leaves. His clothing consists of a blanket only and he carries a white peeled stick. The Izichwe dresses the wound twice daily in the hut and also instructs the initiate in the ways of manhood. The teaching programme continues for about a month. Finally, the boys are taken to a fast-flowing stream where the paint is washed away. They return to the hut naked, where they are smeared with butter, given a new blanket and presented with a black unpeeled stick. After a final talk by a respected elder or relative, the boy becomes a man.

Results

During the December–January period of the 1988/89 Umkhwetha, 45 consecutive young males with the diagnosis "septic circumcision" were admitted to the urological department at this hospital. This figure has no particular significance because the actual number of youths partaking in the Umkwetha and the true incidence of complications are unknown. Penile injury was defined in terms of 4 grades of severity (Table 1) and data on the patients are recorded in Table 2.

Two patients were admitted directly to the Intensive Care Unit (ICU); 1 had been severely beaten with a leather-whip (sjambokked) for refus-

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Table 1 Penile Injury as a Result of Ritual Circumcision: Grades of Severity

Grade 1	Skin loss at base of prepuce with or without laceration of glans or shaft
Grade 2	Marked loss of penile skin
Grade 3	Loss of the glans with or without partial shaft loss
Grade 4	Loss of the entire penis

Table 2 Details of 45 Consecutive Patients Admitted Following Ritual Circumcision

Age (years)	Mean	21 5	(range 16–31)
Mean time between circumcision and admission (days)		18	
Dead on arrival (%)	3/45	(7)	
ICU admissions (%)	2/45	(4)	
Severity of penile trauma			
Grade	*No. of patients*	*(%)*	
1	14	(33)	
2	22	(52)	
3	4	(10)	
4	2	(5)	
	No.	*(%)*	
Immediate surgery	2/42	(5)	
Suprapubic diversion	8/42	(19)	
Antibiotics	28/42	(67)	
Split-skin grafting	8/42	(19)	
Polyarthritis	2/42	(5)	
Mortality	4/45	(9)	

ing to undergo daily penile dressings and had crush syndrome. The other had total necrosis of the penis (grade 4 lesion) with septicaemia and he died within 10 h of admission. The severity of penile injury could be graded in 42 patients; 22 (52%) had marked loss of penile skin (grade 2) and 6 (14%) had grades 3 or 4 lesions; 4 (10%) had lost their glans and in 2 patients (5%) the entire penis was necrotic. One of these died in ICU. The other youth remained quite well despite the presence of the dead organ. Understandably, he could not be convinced that ablation was necessary. Nature, however, took its course and discarded the dead appendage after 10 days. Two patients underwent immediate surgery; 1 required incision and drainage of an inguino-scrotal abscess and the other needed debridement of the glans penis.

Eight patients were diverted by suprapubic push-in catheter. The main indications were severe dysuria, difficulty with micturition as a result of penile tenderness or inability to avoid urine. No suprapubic catheter was required for longer than 4 days. A wide variety of antibiotics was administered by the admitting officers in 67% of the patients. Ampicillin and Ampiclox were the most favoured. Also used in variable combinations were cloxacillin, metronidazole, Bicillin, benzylpenicillin, tetracyclines and gentamicin. Our policy in the urological ward was to stop all antibiotics once the patient was apyrexial. A wide variety of organisms was cultured with no bacteria predominant. One-third of the patients did not receive antibiotic therapy. The mainstay of therapy was thrice-daily penile soakings in dilute Savlon solution followed by dressings with Betadine cream. This regimen succeeded in eliminating local sepsis in almost every case, allowing healing to occur in the vast majority.

Split-skin grafting was required in only 8 patients (19%). The penis showed an amazing propensity for spontaneous healing by advancing fronts of pink, new skin. These fronts originated from the proximal shaft skin edge, around the external urethral meatus and from residual islands of glans or shaft skin and were able to cover a startlingly wide area. Two patients had traumatic distal hypospadias and were advised to return for cosmetic surgery. The surviving patient with total penile loss was referred to a larger centre for reconstructive surgery.

Two patients were noted to have polyarthritis. One had painful effusions of both knees and had a grade 1 penile lesion. The other had inflammation of the left ankle and right wrist and had a grade 2 lesion. Aspiration yielded a sterile serous fluid in both cases. The signs and symptoms resolved spontaneously in each case within a month and we were informed by our orthopaedic collegues that this type of polyarthritis should be regarded as "reactive" or "sympathetic". There were 4 deaths and the mortality rate amongst the 45 youths was 9%.

Discussion

The Umkhwetha is an ancient custom inherent in Xhosa society. It predates the advent of Western values in the African subcontinent by many centuries. It has always been accepted that those who did not survive were not destined to achieve manhood. With the advent of industrialisation in Southern Africa the fabric of tribal society has become increasingly fragile. Methods aimed at reducing the high complication rate should not appear as a Western intrusion into this important custom. Obligatory circumcision in a sterile operating theatre, replacing the Izichwe with a trained doctor or substituting commercial dressings and medicines for the traditional leaves and sheep-skin, would render the Umkhwetha meaningless.

Apart from the management of complications, our role has been to bring the high morbidity and mortality to the attention of the regional Xhosa authority and advise how these could be reduced. We also circumcise boys and youths whenever a legitimate opportunity arises (such as a paraphimosis). Informed consent is essential but rarely is there a refusal. Parents are well aware of possible death and deformity associated with the Umkhwetha. Circumcision for genuine medical reasons is acceptable to the community, whereas any youth who undergoes hospital circumcision by request will be a social outcast.

The spectrum of complications observed over the years is outlined in Table 3. Septicaemia and/or dehydration are frequent causes of mortality. Normal fluid intake is discouraged as a further test of endurance and youths are frequently admitted severely dehydrated.

Rather than the act of circumcision itself, the chief cause of penile injury is the dressing when it is applied too tightly, for too long. The first effect is to compromise the blood supply of the penile skin. With tighter compression the deep dorsal arteries are also occluded and the glans may necrose (Figs 1 and 2). At worst all of the penile vasculature is occluded and the organ is lost.

The penile skin has a remarkable capacity for regeneration, but adjunctive surgical procedures are usually required for excessive skin loss and these include split-skin grafting and mobilising the

Table 3 Complications of Ritual Circumcision

- Death
- Dehydration
- Penile injury
  - Skin loss
  - Amputation
  - Fistula
  - Traumatic hypospadias
  - Traumatic epispadias
- Infection
  - Localised
  - Regional abscess
  - Necrotising fasciitis
  - Septicaemia
  - Septic embolisation
  - Tetanus
  - Gangrene
  - Hepatitis B
  - AIDS
  - Polyarthritis
- Urinary retention
- Healing problems
  - Phimosis (after incomplete circumcision)
  - Meatal stenosis
  - Chordee
- Severe beatings
  - Crush injury
- Psychological disturbance

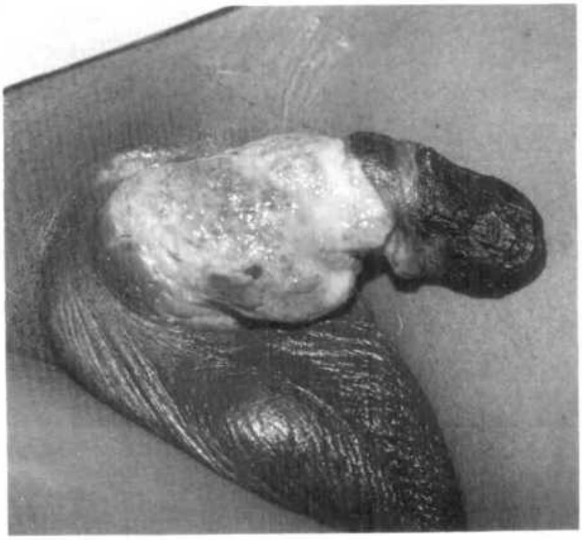

Fig. 1 Septic ritual circumcision with marked loss of shaft skin. The glans is necrotic and about to slough.

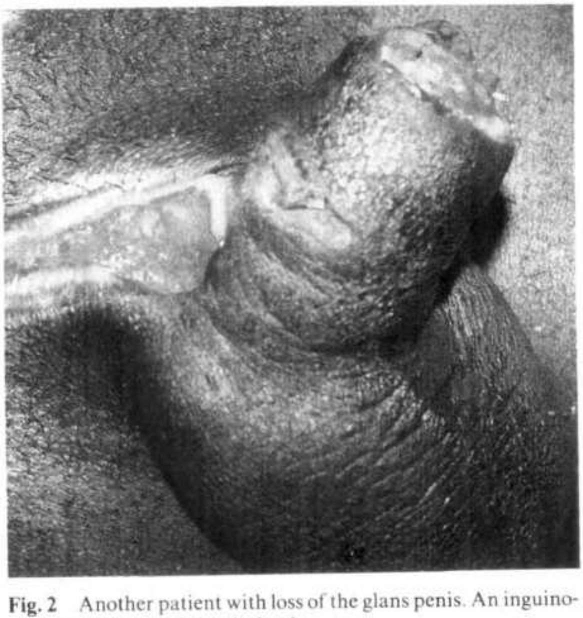

Fig. 2 Another patient with loss of the glans penis. An inguino-scrotal abscess has been drained.

proximal shaft edge to provide distal cover as a sleeve. Occasionally we are faced with a situation of total skin and marked tissue loss that includes most of the pendulous urethra with a fistula at the peno-scrotal junction. For this we have used a technique termed "scrotal gloving". The denuded penile remnant is buried in the scrotum and the neo-glans brought out through a separate incision. The new glans is covered with split skin in an attempt to preserve sensitivity. The urethral fistula is converted into a first-stage urethroplasty by suturing the scrotal skin to the urethral edges. The previous site of emergence of the penile shaft is closed and the scrotum drained. Later, releasing incisions free the newly covered penis from the scrotum and standard hypospadias techniques are employed in an attempt to advance the new meatus. Three of 4 patients who underwent scrotal gloving stated that they had normal sensation, erections and ejaculation, but all had difficulty with penetration because of lack of penile length. The remaining patient had neither sensation nor erectile activity.

All patients had penile sepsis on admission. Our mainstay of therapy was thrice-daily penile soakings in dilute Savlon solution followed by dressings with Betadine cream. This regimen succeeded in eliminating local sepsis in almost every case. Antibiotics were reserved for those with systemic illness and were not administered to apyrexial patients. Several patients were treated for manifestations of septic embolisation such as empyema and soft tissue abscesses. We have also seen cases of tetanus (1 fatal) and serum hepatitis. All patients are now routinely given anti-tetanus toxoid on admission. As yet the youths are not routinely tested for AIDS, but it is a distinct possibility.

A common occurrence is incomplete circumcision. The penis is lacerated and there is severe posthitis and often phimosis. Once sepsis resolves we complete what the Ingcitisi originally set out to do. Meatoplasty may be required for stenoses that develop after urethral trauma or urethroplasty. Skin release or tethering procedures may be required for penile curvature after healing. Discipline in the bush is tough and beatings with a leather-whip (sjambok) are common. We have seen patients with crush syndrome and in renal failure as a consequence. One mildly retarded patient underwent circumcision but refused daily dressings. The severity of his beating can be gauged by the fact that he required both dialysis and ventilatory support for 3 weeks.

Circumcision in the adult may precipitate psychotic delusional behaviour (Ball, 1974; Flaherty, 1980). This is particularly likely when the procedure takes place as part of the Umkhwetha. When penile deformity results, the psychological scars will run deep.

Acknowledgement

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The Authors

I P. Crowley, FRCSE, Head of Department of Urology.
K. M Kesner, FCS(SA)(Urol), Consultant Urologist.

Requests for reprints to: I. P. Crowley, 17 Leadwood Place, Beacon Bay, 5241 East London, Republic of South Africa.

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Case Reports

Transitional Cell Carcinoma Arising in a Ureteric Diverticulum

R. J. PRESCOTT, W. H. RAMSDEN and A. R. MAINWARING, *Department of Pathology, Hope Hospital; Department of Urology, Salford Royal Hospital, Manchester*

Case Report

A 48-year-old male presented with abnormal routine urine cytology. He had worked in the aniline dye industry for 4 years. Subsequent cystoscopy, intravenous and retrograde urography were negative, but a differential ureteric urine sample revealed papillary clusters of atypical transitional cells from the left ureter (Fig. 1).

A left nephroureterectomy revealed 2 ureteric strictures, 2.5 and 1.5 cm long. At these sites the wall was thickened and contained cystic spaces lined by transitional epithelium and surrounded by muscle. In one such diverticulum an early transitional cell neoplasm was seen (Fig. 2).

A post-operative urine sample contained suspicious transitional cells, suggesting similar pathology in the right ureter.

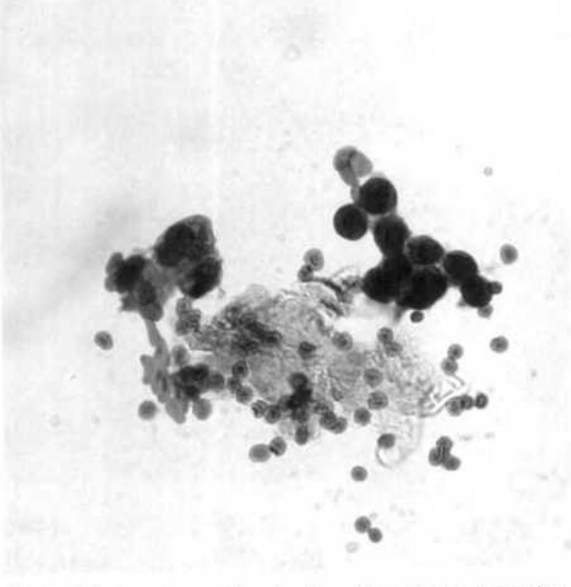

Fig. 1 Cluster of transitional cells with enlarged hyperchromatic atypical nuclei.

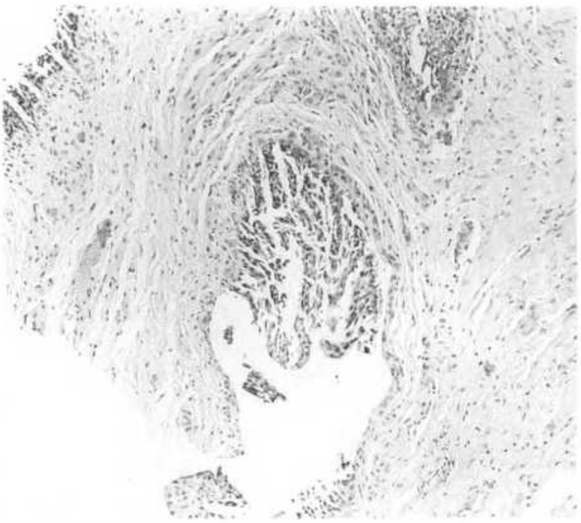

Fig. 2 Ureteric diverticulum surrounded by muscle. The epithelium is heaped and consists of atypical transitional cells representing an early transitional cell neoplasm.

Comment

Ureteric diverticula are round or oval extra-ureteric sacs which open into the ureteric lumen through a stoma. They are also surrounded by a muscle coat (Culp, 1947). A total of 73 cases have been reported prior to 1970 (Crumplin and Jones, 1972) but only 1 showed neoplastic transformation (Harrison, 1983). The tumour in the latter case was a poorly differentiated transitional cell carcinoma with muscle and lymphatic invasion. Surgery and radiotherapy were instituted.

It is interesting that our patient had been exposed to a recognised urothelial carcinogen. Since he recovered well and the neoplasm was pre-invasive, post-operative irradiation was not given. However, this may require reassessment in view of the neoplastic cells found in the post-operative urine.

Although neoplastic transformation of the lining of diverticula is a well described phenomenon, its occurrence in ureteric diverticula is extremely rare.

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Requests for reprints to: R. J. Prescott, Department of Histopathology, Hope Hospital, Eccles Old Road, Salford M6 8HD.

Anterior Urethral Polyp in a Child

A. F. AZMY, *Department of Paediatric Surgery, Royal Hospital for Sick Children, Glasgow*

Case Report

A 5-year-old boy presented with dysuria. He was found to have phimosis and was circumcised. The dysuria persisted and further investigation in the form of intravenous urography and micturating cystourethrography failed to show any abnormality. Urethroscopy revealed a polyp with a long stalk arising from the ventral surface of the anterior urethra (Figs 1 and 2). The polyp was diathermied and complete ablation was achieved on a second attempt.

Comment

Anterior urethral polyps in boys are extremely rare. A review of the English literature has revealed only 4 cases (Redman and Robinson, 1977; Foster *et al.*, 1980; Falkowski and Cook, 1981; Redman, 1982). The polyp was excised transurethrally in 2 children and through urethrotomy in the other 2. The polyp in the present case was diathermied and no tissue was available for histology. Excised polyps in the other reported cases showed a core of fibrovascular tissue covered with transitional epithelium.

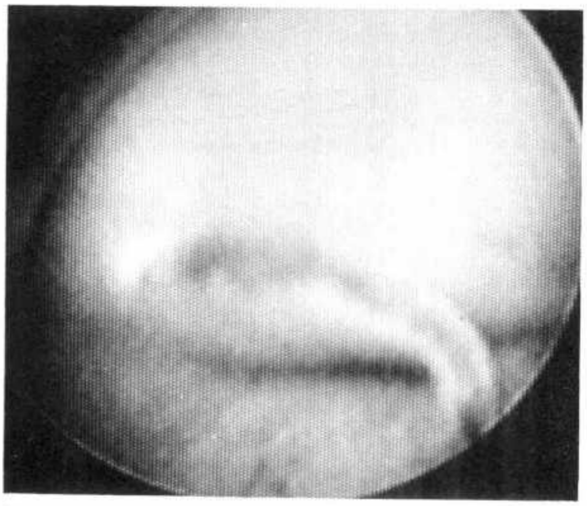

Fig. 1 The polyp.

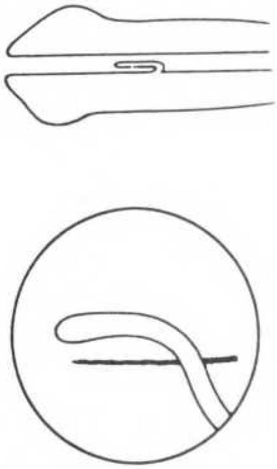

Fig. 2 The site of the polyp.

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Requests for reprints to: A. F. Azmy, Department of Paediatric Surgery, Royal Hospital for Sick Children, Yorkhill, Glasgow G3 8SJ.

Lipomatosis of the Ureter

A. C. THORPE, J. E. MARTIN and B. J. JENKINS, *Department of Morbid Anatomy, The London Hospital, London*

Various benign (Sekar *et al.*, 1980; Bahson *et al.*, 1984) and malignant (Ligthelm and Lister, 1985) non-urothelial tumours of the ureter have been described. We report a case of lipomatosis of the ureter.

Case Report

A 71-year-old man, with known extensive carcinoma of the pancreas, was admitted terminally ill with bilateral bronchopneumonia. Despite intensive physiotherapy and antibiotics he died 3 days after admission.

At post mortem, in addition to the pancreatic carcinoma, was the incidental finding of complete encasement of the left ureter by soft pale tissue extending from renal pelvis to bladder. Histology showed the mass to be composed of mature adipose tissue with foci of lymphocytic infiltration and occasional fibrous septae characteristic of lipomatosis (Fig.). The right ureter was completely normal.

Comment

As far as we are aware, lipomatosis of the ureter has not previously been described. Other non-urothelial tumours of the ureter, such as leiomyoma (Sekar *et al*., 1980), fibroepithelial polyps (Bahson *et al*., 1984), and malignant lymphoma (Ligthelm and Lister, 1985) are recognised, but usually cause loin pain or haematuria. Renal lipomata are well documented and often present with flank pain or a palpable mass; in contrast, our patient had no urological symptoms, the tumour being an incidental finding at post mortem.

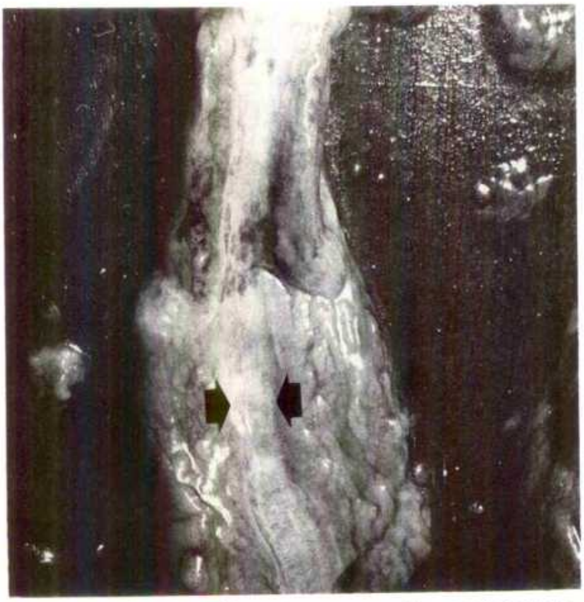

Fig. Mass of mature adipose tissue surrounding normal ureter. Arrows indicate edge of opened ureter.

Acknowledgement

We thank Mr A. D. W. Maclean for permitting us to report this patient.

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Requests for reprints to: J. E. Martin, Department of Morbid Anatomy, The London Hospital, Whitechapel, London E1 1BB.

Juxtatesticular Seminoma

O. DICHMANN, ULLA ENGEL, D. B. JENSEN and T. BILDE, *Departments of Urology and Pathology, Glostrup University Hospital, Glostrup, Denmark*

A case of juxtatesticular seminoma in the epididymis without primary tumour of the testes is reported.

Case Report

A 42-year-old man presented with a 4-month history of pain in the left scrotum. During the same period he had observed 3 nodules. There were no other symptoms. Examination revealed a firm nodular swelling of the left epididymis and a normal testis.

Scrotal exploration revealed a chronic inflamed epididymis with no suspicion of malignancy. The spermatic cord and testis were normal. Epididymectomy was performed. Histological examination revealed a typical seminoma with tumour cells arranged in cords and sheets composed of uniform polygonal cells with round to oval nuclei with prominent nucleoli. The stroma was scanty and infiltrated with lymphocytes (Fig.). Neither epididymal nor testicular structures were identified in this material.

A left orchiectomy, including 7 cm of the spermatic cord, was performed 1 week later. Light microscopy showed an intact atrophic testis with reduced spermatogenesis but no sign of malignancy or carcinoma *in situ* and no evidence of scarring. Epididymal structures were

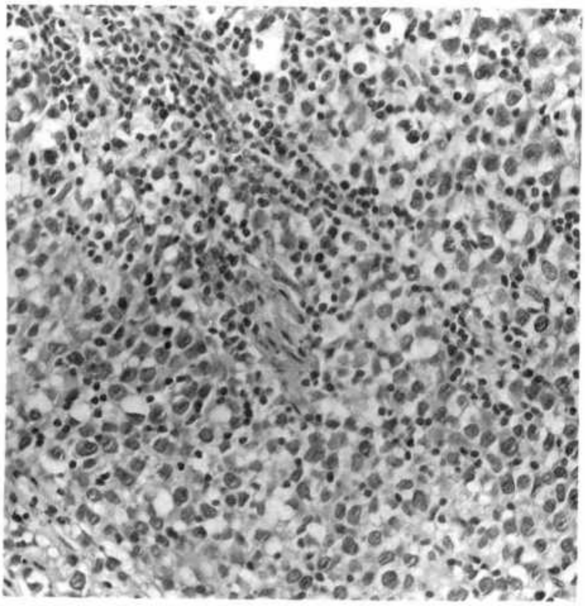

Fig. Seminoma. (H and E × 100).

present showing several foreign body granulomas but no tumour.

Biopsy of the right testis was normal.

The patient underwent post-operative radiotherapy to the regional lymph nodes of the retroperitoneum. At follow-up 2 years later there was no recurrence of tumour.

Comment

Tumours of the epididymis are very rare (Garnick *et al.*, 1982) and are usually benign. No pathological classification has been made (Kissane, 1985). This is the first report of juxtatesticular seminoma in the epididymis. Seminomas outside the testes have been described in the retroperitoneum, mediastinum and gastrointestinal tract by Garnick *et al.* (1982), who suggested that these tumours may originate from totipotent cells which were left during migration of the testes to the scrotum; alternatively, they may be metastases of a primary testicular tumour which has regressed spontaneously.

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Requests for reprints to: O. Dichmann, Regeringsgatan 41, S-37435 Karlshamn, Sweden.

Epididymal Metastasis from Prostatic Carcinoma

A. SNEIDERS and J. E. HELLER, *Department of Urology, St Paul-Ramsey Medical Center, St Paul, USA*

Case Reports

Metastasis to the epididymis was found on bilateral orchiectomy in 2 men, aged 77 and 81 years, with metastatic and locally extensive prostatic carcinoma Gleason grades 4 to 5. In the older patient an asymptomatic left epididymal mass was noted pre-operatively. Both had undergone TURP over 2 years prior to orchiectomy. Immunoperoxidase staining for prostate specific antigen was positive in both cases.

Comment

To the best of our knowledge, there are only 13 reported cases of epididymal metastasis from prostatic carcinoma (Bahnson *et al.*, 1985; Thon *et al.*, 1985). As in our cases, these almost always occurred in patients with locally extensive, poorly or moderately differentiated carcinoma and were usually incidental findings at the time of orchiectomy.

Prostate cancer may disseminate to the epididymis via retrograde lymphatic extension, retrograde flow through the vas deferens or haematogenously. In the case of pre-existing prostate cancer, intraductal retrograde dissemination through the vas deferens may occur at the time of transurethral resection of the prostate.

Epididymal metastasis should be considered in the differential diagnosis of epididymal masses in patients with prostatic carcinoma, especially those with high grade, locally extensive disease. Because of the possibility of leaving behind intrascrotal cancer, Thon *et al.* (1985) recommended against subcapsular orchiectomy for prostatic carcinoma. At a minimum, we feel the epididymis should be carefully examined intra-operatively at the time of orchiectomy. Complete rather than subcapsular orchiectomy should be performed if there is any suspicion of epididymal metastasis.

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Requests for reprints to: J. E. Heller, Department of Urology, St Paul-Ramsey Medical Center, 640 Jackson Street, St Paul, Minnesota 55101–2595, USA.

Recent Change in a Tailgut Cyst Presenting as Urinary Retention

B. M. STEPHENSON, M. BARTLET, R. NIRULA, A. G. EVANS and A. M. REES, *Departments of Surgery and Pathology, Princess of Wales Hospital, Bridgend*

Tailgut cysts are uncommon developmental abnormalities and rarely undergo malignant change. We report the oldest and what we believe to be the first case presenting as urinary retention.

Case Report

An obese 81-year-old man presented in acute urinary retention. He gave a 6-week history of outflow obstruction. Four months previously he had been started on diuretics for lower limb oedema, presumed to be secondary to heart failure, but this had not cleared. Urethral catheterisation drained 800 ml of clear urine. Rectal examination revealed a 40 g benign prostate. His blood urea was 16 mmol/l and creatinine 230 μmol/l.

An attempt at transurethral resection was unsuccessful because of angulation and anterior displacement of the prostatic urethra. The procedure was abandoned and a suprapubic cystostomy performed. Subsequent investigations, including a CT scan (Fig.), confirmed a well defined, partly calcified cystic mass, 13 cm in diameter, arising from the pelvis and extending up to the origin of the inferior vena cava. Both ureters were dilated.

At laparotomy the mass originating from the pre-sacral space was separate from, but displacing the rectum, bladder and prostate. By a combination of sharp and blunt dissection it was removed from its attachment to the lower part of the sacrum.

On the third post-operative day the patient suffered a fatal cerebrovascular accident.

Histology showed a thin-walled cyst filled with mucus, with scanty velvety areas on its inner surface. Only these areas showed any epithelium, which was severely dysplastic. The wall consisted of bland fibrous tissue only, with focal calcification but no muscle component.

Comment

The origin of this mucin-producing cystadenoma is debatable. The possibility that it was a pre-sacral teratoma was discounted by virtue of the patient's age and the lack of a second epithelial type or stromal component. The lack of a primary tumour at post mortem or relevant previous surgery makes a metastatic deposit unlikely. Cystadenomas, at this site, and of Müllerian origin, have been described, but only in females.

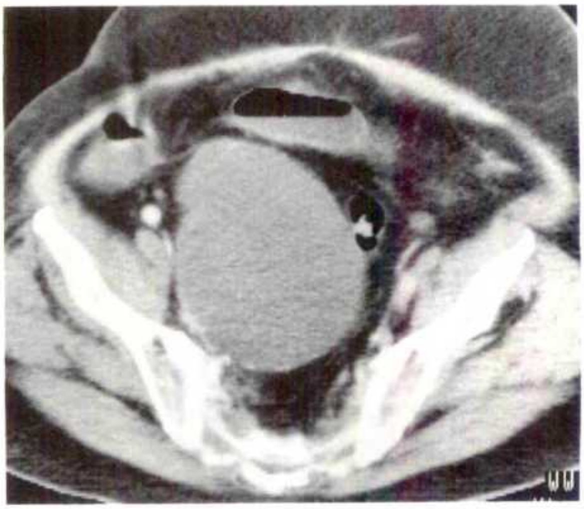

Fig. CT scan of pelvis showing a large, partly calcified cyst lying behind the bladder.

Tailgut cysts are uncommon but recognised entities in this location. The classification of these cysts appears to overlap with that of rectal duplication cysts. Tailgut cysts are believed to be remnants of the embryological tail duct which disappears at the 8 mm stage (Caropreso *et al.*, 1975) and rectal duplication cysts to be "pinched off" remnants (Weitzel and Breed, 1963). Rectal duplication cysts, and not tailgut cysts, are said to possess well defined muscle layers (Weitzel and Breed, 1963; Hjermstad and Helwig, 1988).

We consider a tailgut cyst to be the most likely origin of this tumour, but the lack of residual bowel mucosa precludes a definitive diagnosis.

The cyst had probably been in place for many years and it was only the relatively recent neoplastic transformation that caused marked enlargement and clinical symptoms.

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Hjermstad, B. M. and Helwig, E. B. (1988). Tailgut cysts. *Am. J. Clin. Pathol.*, **89**, 139–147.

Weitzel, R. A. and Breed, J. R. (1963). Carcinoma arising in a rectal duplication. *Ann. Surg.*, **157**, 476–480.

Requests for reprints to: B. M. Stephenson, Coloproctology Research Fellow, Imperial Cancer Research Fund, Genetic Epidemiology Laboratory, 3K Springfield House, Hyde Terrace, Leeds LS2 9LU.

Disappearing Staghorns

M. D. GRIFFITH-JONES, *Department of Urology, Southmead Hospital, Bristol*

Case Report

Mrs B. was 82 years old when she presented in 1986 with bilateral loin pain. She had a coliform urinary tract infection, urea 15 mmol/l and creatinine 220 mmol/l. An abdominal X-ray and intravenous urogram showed large, bilateral staghorn calculi. Serum calcium, phosphate and urate were normal. She was treated with parenteral antibiotics but was thought to be a poor candidate for a major surgical procedure. She was discharged with a recommendation that she take trimethoprim 200 mg each night.

She was reviewed regularly and *Proteus* urinary tract infections, isolated on several occasions, required additional antibiotic therapy. Plain abdominal X-rays, however, showed the gradual disappearance of the staghorn calculi (Figs 1–3). Renal function also improved.

Comment

The reduction in size of staghorn calculi in a patient taking long-term, low-dose trimethoprim has not previously been described. The calculi were undoubtedly induced by infection and although coliforms were identified at this patient's initial presentation, *Proteus* was likely to be the causal organism. By treatment of the infection and eradication of the urea splitting organism, an acid urine is produced and maintained. This is presumed to have been responsible for the stone dissolution in this case.

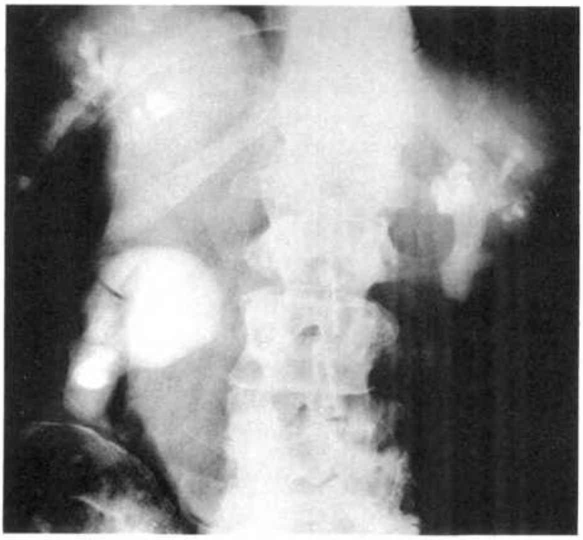

Fig. 1

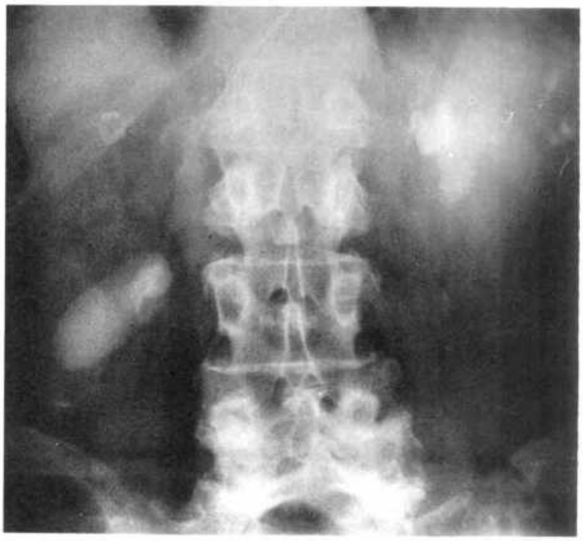

Fig. 2

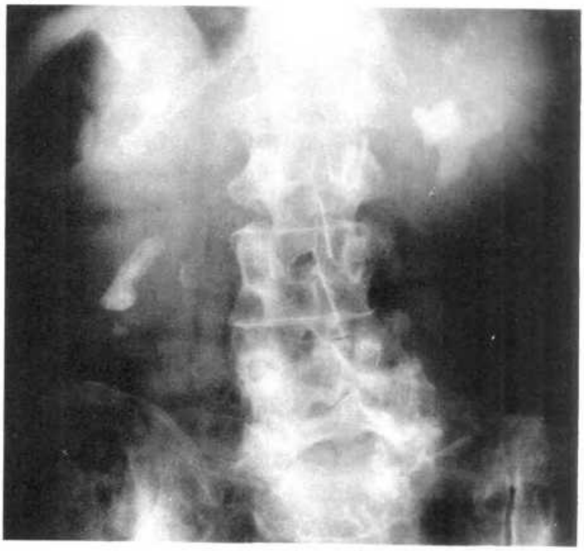

Fig. 3

The preferred treatment for staghorn calculi remains open removal, percutaneous litholapaxy or lithotripsy, but long-term, low-dose antibiotic therapy may have a role post-operatively in preventing recurrence of the staghorn calculi, or in cases where the patient is unfit or unwilling to undergo surgery.

Reference

Lewis, G. A. (1983). Dissolution of renal calculi with Dicloxacillin. *Urology*, **22**, 401–403.

Requests for reprints to M. D. Griffith-Jones, University Department of Obstetrics and Gynaecology, Level 09, Gledhow Wing, St James's University Hospital, Beckett Street, Leeds LS9 7TS.

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Points of Technique

Minimally Invasive Removal of Retained Ureteric Stents

P. G. WHITE and C. EVANS, *Department of Radiology, Royal Infirmary, Cardiff*

Ureteric stents are widely used in the management of benign and malignant ureteric strictures and as an adjunct to lithotripsy and ureteric surgery. Stents are inserted either antegradely or retrogradely and are usually well tolerated. Complications include pain, haematuria, encrustation, ureteric perforation during insertion, stent fracture and stent migration. Whilst downward migration of the stent into the bladder is most likely, upward migration is also recognised (Fig.) and this prevents standard removal via a cystoscope. In this situation, methods of removal include formal exploration, ureterorenoscopy and percutaneous nephrostomy with endoscopic retrieval (Pocock *et al.*, 1986; MacDermott and Gray, 1988).

We have successfully removed stents in 4 patients in whom the stent had migrated up from the bladder.

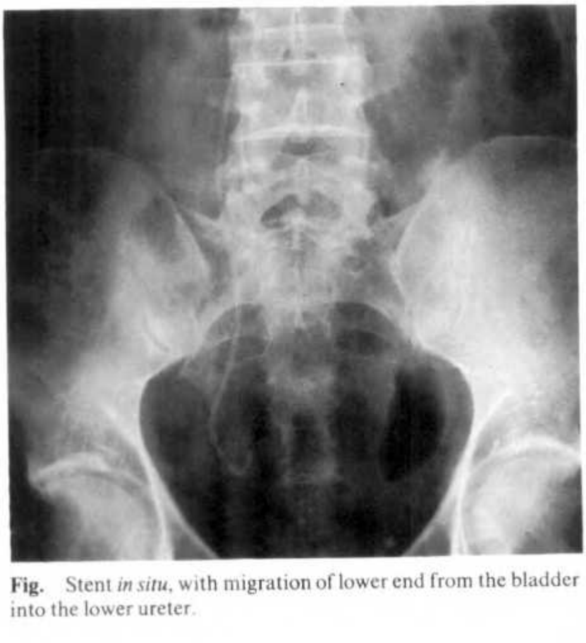

Fig. Stent *in situ*, with migration of lower end from the bladder into the lower ureter.

Technique

With the patient in the prone/oblique position, the collecting system of the kidney is punctured, a wire passed into the renal pelvis and a 9F catheter sheath introducer system (consisting of a tapered dilator within a sheath assembly) is inserted into the renal pelvis. These systems are available from several catheter manufacturers and are in use in most radiology departments that carry out angiography. Various grasping or biopsy forceps may be introduced via the sheath to grasp the stent under fluoroscopic control. The end of the stent need not be grasped (unless encrusted), since the stents are sufficiently flexible and do not break at the point of grasping. After the stent is removed, a small nephrostomy catheter may be left *in situ* to tamponade the track if necessary, but we did not do this. This method was successful in 4 patients but failed in 2 others. One patient had a baggy renal pelvis and we could not grasp the stent. The other patient had a transplant kidney where the ureteric stent had fractured at cystoscopic removal. The puncture of the renal collecting system in this case was not appropriately placed for grasping the retained stent fragment.

Comment

Percutaneous removal of retained stents has been described previously (LeRoy *et al.*, 1986). In their series, stents were removed in 7 of 13 cases via a 24F track using an endoscope under general anaesthesia. In 6 cases the removal was carried out in a manner similar to ours, although larger 10F and 12F sheaths were used in all but 1 case.

The advantages of percutaneous removal of retained ureteric stents under local anaesthesia are obvious. As the use of ureteric stents increases, so complications become more common. This relatively simple method of retrieval should be more widely known and should be attempted before formal track dilatation and nephroscopic removal is attempted.

References

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MacDermott, J. P. and Gray, B. K. (1988). Complications of ureteric pigtail stents. *J. R. Coll. Surg. Edinb.*, **33**, 338–339.

Pocock, R. D., Stower, M. J., Ferro, M. A. *et al.* (1986). Double J stents. A review of 100 Patients. *Br. J. Urol.*, **58**, 629–633.

Requests for reprints to: C. Evans, Department of Radiology, Cardiff Royal Infirmary, Newport Road, Cardiff CF2 1SZ.

The Endoscopic Video Camera as an Aid to the Stamey Procedure

S. C. W. HARRISON and P. H. ABRAMS, *Department of Urology, Southmead Hospital, Bristol*

The Stamey (1973) procedure aims to correct stress urinary incontinence by repositioning the bladder neck. Successful bladder neck elevation depends both on the correct placement of the supporting nylon sutures and their being tied under the correct tension. Accurate suture insertion can be checked by visualising the bladder neck with the needle *in situ*. In Stamey's original description of the operation it was suggested that the sutures be tied with "considerable tension" but it has since been realised that over-tightening should be avoided (Ashken *et al*., 1984). It has become apparent that incontinence will not be controlled if the sutures are too loose, but pain and voiding difficulties may result if they are too tight. Gauging the correct tension is largely a matter of experience. We describe how an endoscopic video system can be used as an aid to tying the sutures under the correct tension; such equipment is now available in many urology operating theatres.

The nylon bladder neck sutures are placed in the normal way via 2 suprapubic incisions. The video camera is attached to a 0° or 30° cystoscope and the surgeon's assistant keeps the bladder neck in view. The surgeon is then able to tie the sutures while watching the video monitor; sufficient tension is applied to elevate the bladder neck but any additional tightening is avoided (Fig.). If a video is not available, the surgeon can watch endoscopically as the assistant ties the sutures to the desired tension.

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Ashken, M. H., Abrams, P. H. and Lawrence, W. T. (1984). Stamey endoscopic bladder neck suspension for stress incontinence. *Br. J. Urol.*, **56**, 629–634.

Stamey, T. A. (1973). Endoscopic suspension of the vesical neck for urinary incontinence. *Surg. Gynecol. Obstet.*, **136**, 547–554.

Requests for reprints to: S. C. W. Harrison, Department of Urology, Southmead Hospital, Westbury-on-Trym, Bristol BS10 5NB.

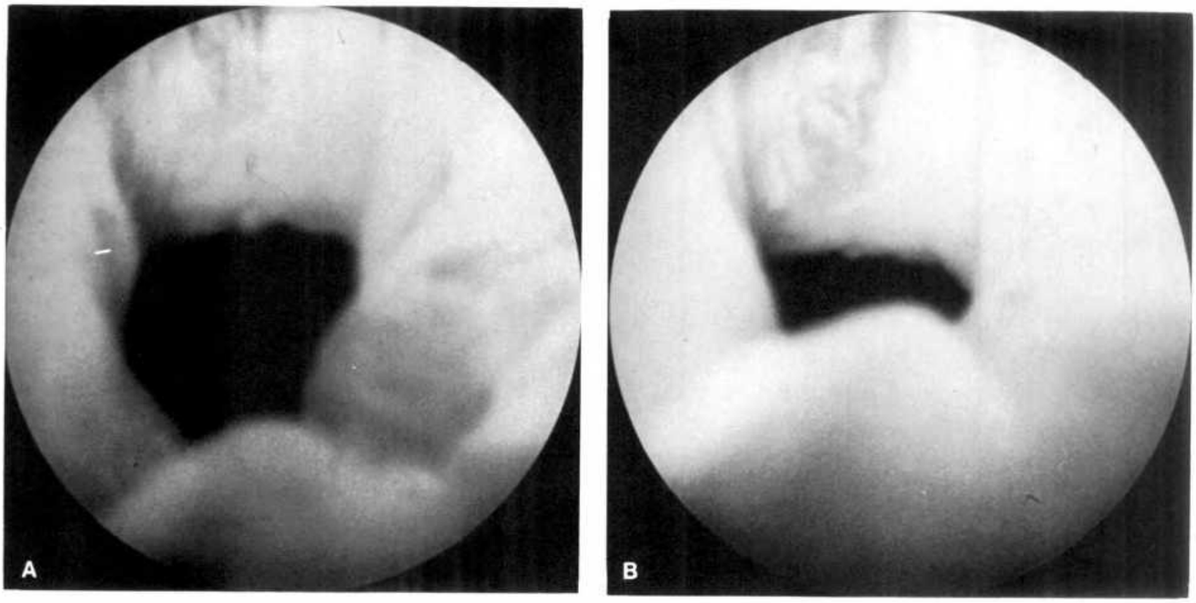

Fig. Endoscopic views of the bladder neck before (A) and after (B) tying the bladder neck sutures. Sufficient tension is applied to elevate the neck of the bladder as shown.

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Correspondence

Dear Sir,

re **The fate of G3pT1 bladder cancer.** B. J. Jenkins *et al. Br J. Urol.*, **64**, 608–610, 1989.

The importance of this paper is not in question: G3pT1 bladder cancer patients are all curable yet many of them will die of their disease. The authors' figures of 25% progression rate and 68% corrected survival at 5 years suggests that their policy of giving radiotherapy is superior to TUR alone when they quote literature rates of 50% for progression and 20% for survival. However, there are a number of gaps and errors in the information they have supplied.

(1) My reading of their results suggests that the progression rate was 32% (17/53).
(2) The sources they quote reveal the following:

Author	*No*	*Progression*	*Survival (crude/ corrected)*	*Time point*
Pocock (1982)	9*	n.s.	12%	5 years
Heney (1983)	27	52%	n.s. (>52%, corrected)	3 years
Jakse (1987)	30	39%	69% crude	5 years
Abel (1988)	24 (G2+G3)	46%	58% corrected	3 years
(Jenkins (1989)	53	32%	64% corrected	5 years)

* median follow-up was 21 months. n.s. = not stated.
References as listed in Jenkins *et al. Br. J. Urol.*, **64**, 608–610.

(3) We are told that *all* patients with G3pT1 tumours at the London Hospital during the time period were treated with radiotherapy. How many of these patients have associated carcinoma *in situ* (CIS), symptomatic or otherwise? Were these included? There are so few patients with this condition treated with radiotherapy in the literature that their outcome would be of more than passing interest.
(4) In addition to the presence of CIS it is important to know the prevalence of such other adverse prognostic factors as multiple tumours and recurrent tumours. Were any patients irradiated with residual exophytic disease in the bladder (having too much to be resected)? What was the outcome when these features were present?
(5) Showing corrected survival is valuable when patients are closely followed but many authors give crude survival, so surely this should be given as well? At the least an indication of the number of patients censored at the relevant time points should be indicated.
(6) Small volume irradiation as used in this study ought to produce few long-term side effects despite the radical dosage. A comment here would have been of interest.

Early treatment with radiotherapy may be the treatment of choice for G3pT1 bladder cancer, saving many lives whilst preserving bladders. The matter remains open, however: it represents a true dichotomy in British urology—the irradiators at present being a fairly small but learned minority. Presumably the majority of urologists are not yet impressed by the benefits of radiotherapy and are concerned by the possibility of toxicity. If we have here "clinical equipoise", should not the role of radiotherapy in G3pT1 disease be formally assessed in a prospective randomised trial?

Yours sincerely,

S. J. Harland
Institute of Urology, 172 Shaftesbury Avenue,
London WC2H 8JG.

Reply by B. J. Jenkins. We thank Dr Harland for his interest in this paper on poorly differentiated superficial bladder cancer treated with radiotherapy. The progression rate of the series was 25% as stated; 13 of the 53 patients, including 4 with secondary carcinoma *in situ*, developed an invasive tumour.

The point of the paper was that G3pT1 tumours are dangerous. In the series of superficial bladder cancers reported by Jakse *et al.* (1987), 11 of 13 patients who died with progressive neoplasia presented with G3pT1 disease. Pocock *et al.* (1982) found that 1 of 9 patients treated by endoscopic means alone were alive at 5 years and that was following cystectomy; 5 patients had died of bladder cancer, 1 of unrelated disease and 2 had a follow-up of less than 1 year. The calculated survival was less than 20% at 5 years. Heney *et al.* (1983) reported that 13 of 27 patients (48%) with G3pT1 disease progressed to invasion. At 2 years, half (3 of 6) of the poorly differentiated T1 tumours described by Abel *et al.* (1988) had invaded muscle.

On reviewing the case notes, 2 patients in the present series had concomitant carcinoma *in situ* and a G3pT1 tumour. They both responded to radiotherapy. No patient in this series was irradiated with residual exophytic disease. No patient in whom the histology report stated a G3pT1 cancer but with a tumour which had been staged as T2 or T3 was included in the study.

A retrospective series that examines symptoms related to radiation may be too vague and subjective for worthwhile analysis. At this time a prospective study designed to assess morbidity following radiotherapy for transitional cell carcinoma of the bladder is being undertaken at the London Hospital. Recently, very encouraging results have been described using intravesical BCG in the treatment of G3pT1 tumours. If a prospective randomised trial is to be performed, perhaps the role of immunotherapy as well as radiotherapy should be assessed.

Dear Sir,

re **The effects of simple hysterectomy on vesicourethral function.** B. T. Parys *et al. Br. J. Urol.*, **64**, 594–599, 1989.

I am particularly interested in the authors' figures on reproducibility of sacral reflex latencies. The figures shown express the range and means for the entire group (n = 9) at two separate assessments. Previous work has suggested that the reproducibility of serially recorded sacral reflexes is unreliable (M. G. Lucas and D. G. Thomas. *Br. J. Urol.*, **63**, 24–27, 1989). In our paper it was the mean variation of subsequent recordings in relation to initial recordings that was expressed and I would be interested to know the results of the authors' measurements, expressed in this way.

Mr Parys states that 11 of 36 hysterectomised women had evidence of a mixed motor/sensory pelvic nerve neuropathy. He can make no conclusions as to whether a motor or sensory defect is present since he did not investigate either long tract sensory conduction by cortical or spinal evoked responses or the integrity of motor fibres by motor unit potential analysis. The finding of raised sensory thresholds has repeatedly been criticised by neurophysiologists and cannot be taken as evidence of a sensory neuropathy since it may represent nothing more than changes in skin/electrode impedance.

There can be little doubt after a simple hysterectomy, in which the pelvic nerves are so obviously at risk, that a pelvic nerve neuropathy accounts for altered vesicourethral function so commonly seen. The results of this study support but do not prove this hypothesis. I am generally concerned about the widespread implication that delayed, or absent, sacral reflex latencies represent evidence of pelvic nerve neuropathy. We know too little about the normal variation of these reflexes and, in particular, the influence of higher centres in modulating their activity to be able to leap to that conclusion. The authors have been careful in their conclusions, but I think it behoves those who write about this methodology to caution the uninitiated into scepticism about the results.

Yours sincerely,

M. G. Lucas
Department of Surgery (Urology), Western General Hospital, Edinburgh.

Reply by B. T. Parys. Thank you for the opportunity to comment on the letter from Mr Lucas.

With regard to the reproducibility of sacral reflex latencies (SRLs); in our series the mean variation of subsequent readings in relation to initial recordings demonstrates a much closer correlation than that of Lucas and Thomas (*Br. J. Urol.*, **63**, 24–27, 1989) (Table).

The reason our figures show better reproducibility may be due to two factors. Firstly, all of our patients were neurologically normal, unlike the spinal injury patients, in whom subtle but clinically occult changes may occur between assessments. Secondly, all investigations were performed and evaluated by one person, thus minimising any variations in interpretation.

Alterations in sensory thresholds may occur because of changes in skin/electrode impedance, but in the current state of knowledge it is equally possible that these may truly reflect sensory changes. Therefore it is entirely reasonable, in the absence of more direct methods of pelvic nerve assessment, to infer the possibility of a mixed motor/sensory neuropathy in those patients with prolonged latencies and significant threshold evaluation.

In view of the paucity of information about normal variations of these reflexes, I agree that those using SRLs must take care in the conclusions that are drawn.

Table Mean Variation of Subsequent Recordings in Relation to Initial Recordings

		%	*ms*
Latencies	DN–US	3.8	1.3
	DN–AS	4.1	1.4
	US–AS	3.2	2.0
		%	*Volts*
Thresholds	DN	6.5	1.7
	US	5.2	1.3

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Notices

British Association of Urological Surgeons

President: R. E. Williams, MD, ChM, FRCS, FRCSE

Annual Meeting: Glasgow. 25–28 June 1991

Abstracts of contributions to be considered as either papers, posters or videos by the Programme Sub-Committee of Council should be submitted on the special forms available from the BAUS Secretariat. Completed forms, which should state clearly whether the submission is a paper, a poster or a video, must be returned to the Honorary Secretary by Friday, 4 January 1991.

Abstracts not on the special forms will NOT be considered.

All correspondence to: R. J. Morgan, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

British Association of Urological Surgeons

Autumn Meeting. Medical School, Queen's Medical Centre, University Hospital, Nottingham. 5 and 6 October 1990

The Day Meeting of the Association on 6 October will be preceded by a post-graduate teaching afternoon on 5 October, when the topic will be 'Impotence and Infertility'.

Further information from: M. C. Bishop, Department of Urology, City Hospital, Nottingham NG5 1PB.

C.-E. Alken Prize

An endowment fund has been established to further clinical work and research in the field of Urology by presenting an annual award of SwF 10,000 for outstanding scientific endeavours. The award will be for an unpublished work in the field of Urology. An award certificate will also be presented. The prize money may be divided among several contributors.

The papers may be written in either German or English and three copies must be submitted by 30 September 1990 to: Stiftungsrat C.-E. Alken-Stiftung, Advokaturbüro Dr F. Kellerhals, Bundesplatz 4, CH-3011 Bern, Switzerland.

Each submission must be affixed with a code word and must not bear the author's name. In addition, a sealed envelope labelled with the code word is to be included, containing on a separate sheet of paper the author's name and professional standing, together with the code word.

The adjudicators for the award will be the Board of Directors of the endowment fund and their decision will be final.

The Surgitek Prize

The Prize consists of a fully sponsored visit to the American Urological Association Annual Five-day Meeting, together with a tour of Surgitek's manufacturing facility in Racine, Wisconsin. It is open to trainees in urology and consultants who are within 5 years of first appointment. Entrants should submit a written paper, which may be on any subject, but must be unpublished, and must not have been submitted previously for the Surgitek Prize, or other prizes. The winning entry will be the one which is considered to be "The most significant contribution to urology".

Entries will be judged by three members of BAUS Council nominated at the October meeting of Council. Papers should be submitted in triplicate to the Honorary Secretary by 1 January each year.

Addenda

re Voiding patterns in men evaluated by a questionnaire survey P. Sommer *et al. Br. J Urol.*, 65, 155–160, 1990.

All of the decade numbers in the above article should be increased by 1, *i e* the second decade should be the third decade, the third decade should be the fourth, *etc* The authors apologise for this unfortunate error

re Cystitis glandularis—reversal with intravesical steroid therapy P. Holder *et al. Br J. Urol*, 65, 547–548, 1990.

The illustrations in the above article have been wrongly numbered, *i.e* Figure 2 should be Figure 1 and *vice versa*. The printers apologise for this mistake

British Journal of Urology (1990), 66, 333–334

Diary

1990

October 1–4	92nd Congress of French Urology. Paris. Contact Convergences, Eurochirurgie—A.F.C. 90, 120 Avenue Gambetta, 75020 Paris, France.
October 4–5	Urological Management of Spinal Injury. Institute of Urology, London. Contact Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 01 240 9115.
October 5–6	BAUS Autumn Meeting, City Hospital, Nottingham. Contact BAUS office.
October 11	Female Incontinence Update, Derby City Hospital. Contact: Mr C. P. Chilton, Derby City Hospital, Uttoxeter Road, Derby DE3 3NE.
October 12	Urological Consequences of Major Pelvic Surgery, Birmingham. Contact: Miss J. Snowden, Department of Urology, Queen Elizabeth Medical Centre, Birmingham B15 2TH. Tel: 021-472 1311, Ext. 3287.
October 16–19	25th Annual Meeting of the Egyptian Urological Association. Cairo, Egypt. Contact Dr Ahmad S. Bedair, 26 Adly Street, Flat 908, Cairo, Egypt.
October 17–19	Advanced Stone Management Course. Institute of Urology, London. Contact Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 01 240 9115.
October 17–19	25th Annual Meeting of the Egyptian Urological Association, Cairo. Contact: The Congress Secretary Ahmad Samy Bedair MD, 26 Adly Street, Flat 908, Cairo, Egypt.
October 25–26	Urological Management of Spinal Injury, Institute of Urology, London. Contact: Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115.
October 25–29	Second International Congress on "The Pelvic Floor"—Update Management. Fort de France, Martinique. Contact Bureau Congress: I.F.R.U G. "The Pelvic Floor", 2 Square La Fontaine, 2, Paris 75016, France.
November 8–9	Renal Failure and Transplantation. Guy's Hospital, London. Contact Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 01 240 9115.
November 10	Basic Science and Urology Symposium, Glasgow. Contact Mr R Scott, Department of Urology, Royal Infirmary, 16 Alexandra Parade, Glasgow G31 2ER.

1991

January 4	Final date for submission of abstracts for 1991 BAUS Annual Meeting.
January 22–25	Eighth Copenhagen Symposium on Endoscopic Urological Surgery. Herlev Hospital, Herlev, Denmark. Contact F. Rasmussen, Department of Urology, Herlev Hospital, 2730 Herlev, Denmark.

February 3–6	International Conference on Orgasm. New Delhi, India. Contact Professor Prakash Kothari, First International Conference on Orgasm, 203 A, Sukhsagar. N. S. Patkar Marg, Bombay 400 007, India.
February 23–March 2	Royal Society of Medicine, Section of Urology, Vail, Colorado. Contact: M. H. Ashken, Consulting Rooms, BUPA Hospital, Old Watton Road, Colney, Norwich NR4 7SZ.
April 12–13	Second Meeting of European Society of Paediatric Urology, Beaune, France. "Neurogenic Bladder in Children and Adolescents". Contact: Dr P. Mouriquand, "Le Dizenier", 11 Impasse Mouillard, 69009 Lyon, France.
June 2–6	American Urological Association, Metro Toronto Convention Centre, Toronto, Canada.
June 7–8	Fourth Pediatric Surgery Research Workshop, Berlin, Germany. Contact: Dr F. Schier, Pediatric Surgery, Univ.-Klinikum Steglitz, Hindernburgdamm 30, 1000 Berlin 45, Germany. Tel: (0 30) 7 98 41 81/29 09.
June 16–20	Canadian Urological Association Annual Meeting, Ottowa. Contact: Dr R. B. Auld, Suite 620, 5991 Spring Garden Road, Halifax, Nova Scotia, Canada B3H 1Y6.
June 25–28	BAUS Annual Meeting, Scottish Exhibition and Conference Centre, Glasgow. Contact: BAUS office.
September 1–6	6th World Congress in Ultrasound, Copenhagen. Contact: Spadile Congress Service, Sommervej 3, DK-3100 Hornbaek, Denmark. Tel: 45 2 20 24 96.
September 4–7	Twenty-first Congress of the International Continence Society. Budapest, Hungary. Contact A. Tankó, Üllõi ut 78/b, Department of Urology, Semmelweis Medical School, H-1082 Budapest, Hungary. Tel: (36) 1 1139 016.

1992

January 10	Final date for submission of abstracts for the 1992 BAUS Annual Meeting.
May 10–14	American Urological Association, Washington Convention Centre, Grand Hyatt, Washington DC.
June 21–26	BAUS Annual Meeting, Bournemouth International Centre, Bournemouth. Contact: BAUS Office.
June 22–25	Canadian Urological Association Annual Meeting, Winnipeg. Contact: Dr R. B. Auld, Suite 620, 5991 Spring Garden Road, Halifax, Nova Scotia, Canada B3H 1Y6.
August 24–27	Third European Symposium on Uroradiology. Herlev, Denmark. Contact Dr H. S. Thomsen, Department of Diagnostic Radiology 54E2, Herlev Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark.

1993

May 16–20	American Urological Association, San Antonio Convention Centre, San Antonio, Texas.
June 13–17	Canadian Urological Association Annual Meeting, Toronto. Contact: Dr R. B. Auld, Suite 620, 5991 Spring, Garden Road, Halifax, Nova Scotia, Canada B3H 1Y6.

1994

May 15–19	American Urological Association, Moscone Centre, San Francisco, California.

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Book Reviews

Combination Therapy in Urological Malignancy (Clinical Practice in Urology Series). Edited by P. H. Smith. Pp. xiii+278. London, Berlin, Heidelberg, New York, Paris, Tokyo: Springer-Verlag. 1989. Price: DM 192.–.

The urologist is well aware of the limitations of surgical treatment of urological cancer, and close collaboration with radiotherapists and oncologists has been a hallmark of the successful advances that have been made in recent years. Much has changed since a previous edition of this series, entitled "Chemotherapy and Urological Malignancy", was published in 1982. In this new edition, Philip Smith has broadened horizons to include radiotherapy and hormone treatment, local and systemic immunotherapy, in addition to chemotherapy. Successful integration of these treatment modalities is obviously vitally important and this is the subject of the opening chapter by Shipley from Boston. The treatment of carcinoma of the kidney, superficial and invasive bladder tumours, prostate cancer, testicular tumours and penile carcinoma are all considered from the point of view of combining therapies of known or possible efficacy to obtain maximum benefit.

The results are evaluated critically throughout, but most brilliantly in an acerbic analysis by Raghavan from Sydney, entitled "Clinical trials . . what have they achieved?" Quality of life after treatment, effective palliation when all hope of cure has gone and—needless to say—the cost of treatment are all dealt with in satisfying detail. The chapters are crammed full of up-to-date information, well laid out and generously referenced. This book is a must for the practising urologist with an interest in urological cancer and an eye to the future

Shock Wave Lithotripsy. State of the Art. Edited by J. E. Lingeman and D. M. Newman. Pp. xiii+417. New York: Plenum Press. 1988. Price: US $85.00.

This book reports material presented at the Methodist Hospital of Indiana's Fourth Annual Symposium on Shock Wave Lithotripsy, held in Indianapolis in March 1988. Following an introduction by Christian Chaussy, there are 6 parts devoted to management of ureteric calculi, large calculi, ESWL treatment results, gallbladder calculi, second generation machine results and a research forum.

The book contains a wealth of useful information and has been well edited, although there is inevitable overlap and repetition related to the number of contributions. For those considering purchase of a machine there is an excellent study comparing the advantages and disadvantages of 7 clinically effective second generation machines. Since this book was published, the conclusion that ultrasound and X-ray imaging are complementary has been taken up by the manufacturers in that machines incorporating both imaging modalities are now being marketed This fact illustrates how quickly this field is moving and how quickly published material appears dated. "State of the art" is a difficult term to sustain.

Prostatic Disorders. Edited by D. F. Paulson. Pp. xiv+383. Philadelphia, London: Lea & Febiger. 1989. Price: £27.50.

The opening 3 chapters cover anatomy, imaging and urodynamic evaluation and they provide a splendid start to this book

In an embracing title such as this, the reader can anticipate full coverage of inflammatory disease, benign prostatic hyperplasia and prostatic carcinoma—and he/she will not be disappointed.

This is a comprehensive text with 22 chapters written by well known authorities. Included in the inflammatory disease section are chapters on zinc and the prostate and pelvic pain.

In the section on benign prostatic hyperplasia there is a useful chapter on pharmaceutical management of benign prostatic hyperplasia but notably absent from this section is any reference to other methods of management of the prostate such as heating, cooling, prostatic stents or balloon dilatation. Also, it was disappointing to see no reference to the current interest in late morbidity after transurethral resection of the prostate.

The first chapter in the prostate cancer section refers to diagnostic dilemmas and the problems in the use of markers and other diagnostic technologies. The changes in the TNM classification between 1978 and 1987 have left predictable confusion (pages 316, 330) which requires the reader to remain alert.

This book is highly recommended as a reference source for all prostatic disorders.

Urolithiasis. Edited by V. R. Walker, R. A. L. Sutton, E. C. B. Cameron, C. Y. C. Pak and W. G. Robertson. Pp. xxv+1066. New York, London; Plenum Press. 1989. Price: US $145.00.

This is the latest report of the Renal Stone Research Symposium Series which originated with the meeting in Leeds in 1968, at which time it was the inspiration of Mr Leslie Pyrah; the first book of the series was edited by Hodgkinson and Nordin. The modest 332 pages of the original work are almost overwhelmed by the encyclopaedic nature of the present volume.

A comparison of the content between the two books indicates the extent and ingenuity of research and research techniques that have occurred in the meantime. This most recent meeting, which was in Vancouver in 1988, some 20 years on from the first meeting, allowed a fitting tribute to Birdwell Finlayson, who had died shortly before. His contribution to the physico-chemistry of stone formation was unparalleled and he also contributed significantly to surgery, kidney transplantation and, most recently, to the new forms of stone management including lithotripsy. The book contains a tribute to his memory and his work

Just as in the first published account of this symposium series, so in this book the epidemiology of stone remains to fascinate and to teach; 130 pages are devoted to this theme and the subject is dealt with in depth, not confining itself merely to observation of distribution but also enquiring into biochemical and other factors that are directly related.

It is interesting to see that the main thrusts of current research have their origins 20 years ago and this is perhaps salutary, for the inference from this is that, despite modern advances, there are still these originally conceived problems to be solved. There is, of course, much greater sophistication in the research work; epithelial transport mechanisms are considered at the intracellular level and there is also investigation of cellular mechanisms in intestinal epithelial transport of stone constituents. At first sight, for the stone researcher of a clinical lifetime, there is much here which is *déjà vu*, but this is probably unfair, bearing in mind that the depth of investigation is so much greater and the techniques that much more sophisticated. It remains a fascinating account of a theme of surgical research that has become the more significant with the realisation that the manifestation of idiopathic stone disease is also the indicator or marker of the predisposition to other diseases of Western civilisation. This is perhaps not appreciated as much as it ought to be.

No book on urolithiasis could now be complete without the recognition of the latest advances in surgical management. This is the main departure from the model of previous volumes reporting these meetings. Nearly 200 pages are devoted to the new minimally invasive and non-invasive management of stone and the results achieved by a variety of lithotriptors, percutaneous and endoureteric techniques. This incursion into a previously almost entirely scientific treatise is significant. It may be the writing on the wall signalling the end of stone research as we have known it these last 20 years. Certainly both in the United States and in the United Kingdom, grant-giving bodies are more reluctant to devote their funds to this type of research in the face of the consistent effectiveness of these new forms of therapy.

This book provides a comprehensive account of the state of the art at this time.

Atlas of Urologic Surgery. By F. Hinman, Jr. Pp. xxix+1057. Philadelphia: Saunders. 1989. Price: £118.00.

Frank Hinman, Jr., with his artist P. C. Stempler, has combined very successfully the merits of the one-author, one-artist textbook with those of the multi-authorship ones, which so often suffer from wide variations in the content and quality of text and figures. He has accomplished this by sending each completed chapter with its illustrations to friends or colleagues who are acknowledged experts on the operations described therein and asked them to add or delete anything they consider appropriate and to provide a commentary which is included in the text at the conclusion of each chapter The names of the 200 colleagues who have helped in this way are listed at the front of the book.

The book describes only open operations, covering comprehensively the penis, urethra, prostate, bladder, ureter, kidney and adrenal, and excludes all endoscopic and percutaneous procedures. The book concludes with a chapter entitled "Urologists' Workshop", which discusses sutures, staples and stents and describes operations which are not, strictly speaking, urological but may have to be done by urologists; these include intestinal anastomoses, herniorrhaphy, repair of vascular injuries and some plastic procedures. There is an extensive list of references to both books and audio-visual presentations.

Even a casual glance at some of the 1057 pages of this book will reassure the most pessimistic of those urologists who fear that all urological procedures will become either endoscopic or percutaneous within the next decade. The author, the artist, the publishers and the printers are to be congratulated on producing this magnificent book, which should be available to all urologists, trained and training.

Books Received

Acyclovir Therapy for Herpesvirus Infections (Infectious Diseases and Therapy Series, Volume 4). Edited by D. A. Baker. Pp. xv+323. New York, Basel: Marcel Dekker. 1990. Price: $99.75 (USA and Canada); $119.50 (all other countries).

Prevention of Progressive Uremia. Volume 1. Edited by E. A. Friedman, Monica Beyer, Natale G. DeSanto and C. Giordano. Pp. xiii+179. New York: Field & Wood. 1989. Price: £48.50.

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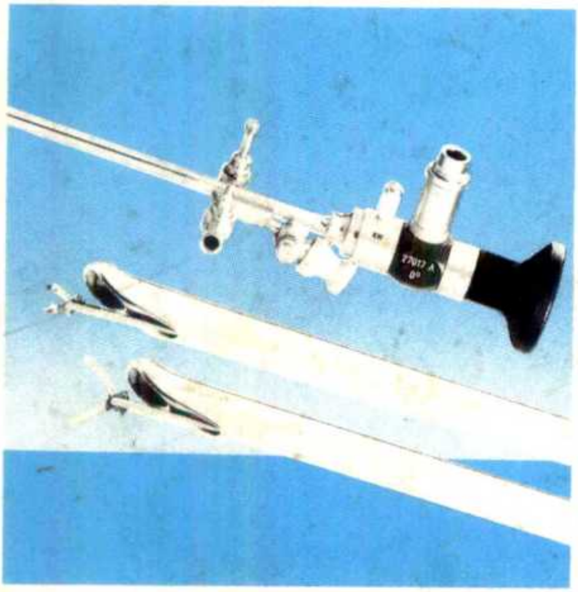

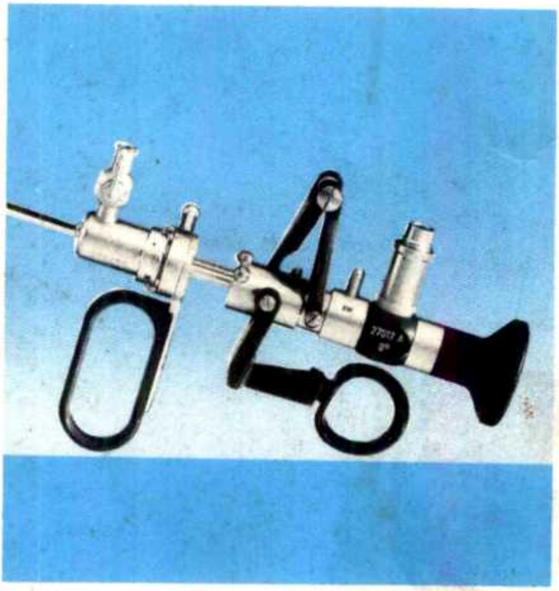

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Cable: Endoskopie
Phone (0 74 61) 70 80, Telex: 762 656 storz d
Teletex: 746 118, Telefax: (0 74 61) 70 81 05

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